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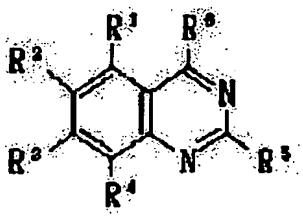
(54) NITROGEN-CONTAINING HETEROCYCLIC COMPOUND

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject compound, having inhibiting activities against cyclic guanosine 3',5'-monophosphate(cGMP) phosphodiesterases and effective against various ischemic cardiac diseases, etc.
SOLUTION: This compound is represented by formula I [R1 to R4 are each H, a halogen, a (halogen-substituted)



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lower alkyl, a (substituted)cycloalkyl, etc.; R5 is H, a halogen, OH group, hydrazino, a lower alkyl, etc.; R6 is H, a halogen, OH group, amino, a lower alkyl, etc.], e.g. 4-chloro-6-cyanoquinazoline. Furthermore, the compound is preferably obtained by reacting, e.g. a quinazoline derivative represented by formula II with phosphorus oxychloride, or reacting the quinazoline derivative with phosphorus oxychloride in the presence of phosphorus pentachloride and heating the reactional mixture, etc. In the case of oral administration, the daily dose thereof for an adult is usually preferably about 1-1000mg administered in one to three divided portions.

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Drawings are not displayable due to the volume of the data (more than 200 drawings).

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The following general formula (1) The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology.
[Formula 1]
They are the inside of [type, that R1, R2, R3, and R4 are the same or the low-grade alkyl group which may be permuted by the hydrogen atom which is different from each other, the halogen atom, and the halogen atom and the cycloalkyl radical which may be permuted, a lower alkoxy group, a hide ROKISHI alkyl group, a nitro group, a cyano group, the acylamino radical, the carboxyl group that may be protected, and a formula [** 2].
(— R7 means a low-grade alkyl group among a formula, and n means the integer of 0, or 1-2.) — the radical shown or formula [** 3]
(The inside of a formula, that R45 and R46 are the same or the hydrogen atom which is different from each other, or a low-grade alkyl group is meant.) R45 and R46 It becomes together with the nitrogen atom which they have combined, and the ring which may contain another nitrogen atom and the oxygen atom can be formed. Moreover, this ring may be permuted. The radical shown is meant. Moreover, two may become together [of R1, R2, R3, and R4], and methylene dioxy, ethylene dioxy, or a phenyl ring may be formed. R5 is the hydrogen atom, halogen atom, hydroxyl-group, hydrazino radical, low-grade alkyl group, and cycloalkyl radical which may be permuted, a lower alkoxy group, a low-grade alkenyl radical, the carboxy alkyl group that may be protected, the carboxy alkenyl radical which may be protected, a hide ROKISHI alkyl group, the carboxyl group which may be protected, and a formula [** 4].
(— R8 means a low-grade alkyl group among a formula, and m means the integer of 0, or 1-2.) — the radical shown, the radical shown by formula-O-R9 (R9 means among a formula the hide ROKISHI alkyl group which may be protected, the carboxy alkyl group which may be protected, or the benzyl which may be permuted.), and formula [** 5]
(— R23 means a hydroxyl group, a low-grade alkyl group, a lower alkoxy group, a hide ROKISHI alkyl group, or a hide ROKISHI alkyloxy radical among a formula.) — the radical shown — The hetero aryl group which may be permuted, 1 which may be permuted, 3-benzodioxolyl radical, 1 which may be permuted, 4-benzodioxolyl radical, 1 which may be permuted, 3-benzodioxolyl alkyl group, The inside of 1 which may be permuted, 4-benzodioxolyl alkyl group, and a formula-C (R24) =X [type, and X are oxygen atom, sulfur atom, or formula =N-R10 (the inside of a formula and R10 mean a hydroxyl group, a cyano group, or the carboxy alkyloxy radical that may be protected.). the radical shown is meant — R24 means a hydrogen atom or a low-grade alkyl group.] The radical come out of and shown, or formula - NR 11R12 (R11 and R12 mean among a formula same or hydrogen atom [which is different from each other], low-grade alkyl group, and hide ROKISHI alkyl group, amino alkyl group, carboxy alkyl group [that may be protected], alkyl carbamoyl group, carboxy alkyl carbamoyl group [which may be protected], heteroarylalkyl radical [which may be permuted], 1, and 3-benzodioxolyl alkyl group or 1, and 4-benzodioxolyl alkyl group.) Furthermore, R11 R12 It becomes together with the nitrogen atom which they have

combined, and the ring which may contain another nitrogen atom and the oxygen atom can be formed. Moreover, this ring may be permuted. The radical shown is meant. R6 is a hydrogen atom, a halogen atom, a hydroxyl group, the amino group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkenyl radical, 1, 3-benzodioxolyl alkyloxy radical, 1, 4-benzodioxolyl alkyloxy radical, the phenyl alkyloxy radical that may be permuted, and a formula [** 6].
(R13 and R14 mean among a formula the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group.) Furthermore, R13 and R14 It may become together and methylene dioxy or ethylene dioxy may be formed. The radical shown, formula [** 7]
(The inside of these formulas, that R15 and R16 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Further R15 R16 may become together and may form methylene dioxy or ethylene dioxy. A piperidine-4-spiro-2'-dioxane-1-IRU radical, formula [** 8]
(The inside of a formula, that R48 and R49 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Furthermore, R48 and R49 may become together and may form methylene dioxy or ethylene dioxy. Z means a sulfur atom or an oxygen atom. s means the integer of 0, or 1-8. The radical shown, formula [** 9]
(-- R50 means among a formula a hydroxyl group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, the carboxyl group that may be protected, a cyano group, a hide ROKISHI alkyl group, or a carboxy alkyl group.) -- the radical shown and formula [** 10]
R17 means among [type the hydrogen atom, low-grade alkyl group, acyl group, low-grade alkoxyalkyl group, and carboxy alkyl group which may be protected, or a hide ROKISHI alkyl group. Y is the radical shown by formula-(CH2) q- (q means the integer of 0, or 1-8 among a formula), or a formula [** 11].
It comes out and the radical shown is meant. Furthermore, it is formula-(CH2) q. - In the radical shown, when q is the integer of 1-8, each carbon may have 1-2 substituents. R18 means a hydrogen atom, a hydroxyl group, the carboxyl group that may be protected, a cyano group, an acyl group, the hetero aryl group that may be permuted, or the cycloalkyl radical which may be permuted.] The radical come out of and shown, or a formula [** 12]
(R19 means among a formula a hydrogen atom, a low-grade alkyl group, a low-grade alkoxyalkyl group, an acyl group, the carboxy alkyl group that may be protected, or a hide ROKISHI alkyl group.) R20, R21, and R22 mean a same or hydrogen atom [which is different from each other], halogen atom, hydroxyl-group, amino-group, nitro group, low-grade alkyl group, lower alkoxy group, low-grade alkoxyalkyl group, and low-grade alkenyl radical, an acyl group, the acylamino radical, an alkyl sulfonylamino radical, a hide ROKISHI imino alkyl group, an alkyloxy carbonylamino radical, alkyloxy carbonyloxy group, or the hetero aryl group that may be permuted. Moreover, two of R20, R21, and R22 can form the ring of the saturation which may become together and may contain the nitrogen atom, the sulfur atom, or the oxygen atom, or partial saturation. r means the integer of 0, or 1-8. The radical shown is meant. R6 [however,] -- the following type (i) (ii) -- or (iii) The case where it is the radical shown is removed.
[Formula 13]
(R19 has above semantics among a formula.) R25 means a halogen atom. R26 A lower alkoxy group is meant. R27 A hydrogen atom, a halogen atom, a nitro group, a low-grade alkyl group, or a lower alkoxy group is meant. R28 A hydrogen atom or a low-grade alkyl group is meant. y Mean the integer of ** 1-4. z Mean ** 1 or 2.]
[Claim 2] The following general formula (2) The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology.
[Formula 14]
R1, R2, R3, R4, and R5 have above semantics among [type. R6' A hydrogen atom, a halogen atom, a hydroxyl group, the amino group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkenyl radical, 1, 3-benzodioxolyl alkyloxy radical, 1, 4-benzodioxolyl alkyloxy radical, the phenyl alkyloxy radical that may be permuted, formula [** 15]
(R13 and R14 mean among a formula the same or the hydrogen atom which is different from

each other, a low-grade alkyl group, or a lower alkoxy group.) Furthermore, R13 and R14 It may become together and methylene dioxy or ethylene dioxy may be formed. The radical shown, formula [** 16]
(The inside of these formulas, that R15 and R16 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Further R15 R16 may become together and may form methylene dioxy or ethylene dioxy. A piperidine-4-spiro-2'-dioxane-1-IRU radical, formula [** 17]
(The inside of a formula, that R48 and R49 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Furthermore, R48 and R49 may become together and may form methylene dioxy or ethylene dioxy. Z means a sulfur atom or an oxygen atom. s means the integer of 0, or 1-8. The radical shown, formula [** 18]
(— R50 means among a formula a hydroxyl group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, the carboxyl group that may be protected, a cyano group, a hide ROKISHI alkyl group, or a carboxy alkyl group.) — the radical shown and formula [** 19]
R17 means among [type the hydrogen atom, low-grade alkyl group, acyl group, low-grade alkoxyalkyl group, and carboxy alkyl group which may be protected, or a hide ROKISHI alkyl group. Y is the radical shown by formula-(CH2) q- (q means the integer of 0, or 1-8 among a formula), or a formula [** 20].
It comes out and the radical shown is meant. Furthermore, it is formula-(CH2) q. - In the radical shown, when q is the integer of 1-8, each carbon may have 1-2 substituents. R18 means a hydrogen atom, a hydroxyl group, the carboxyl group that may be protected, a cyano group, an acyl group, the hetero aryl group that may be permuted, or the cycloalkyl radical which may be permuted.] The radical come out of and shown, or a formula [** 21]
(R19 means among a formula a hydrogen atom, a low-grade alkyl group, a low-grade alkoxyalkyl group, an acyl group, the carboxy alkyl group that may be protected, or a hide ROKISHI alkyl group.) R20, R21, and R22 mean a same or hydrogen atom [which is different from each other], halogen atom, hydroxyl-group, amino-group, nitro group, low-grade alkyl group, lower alkoxy group, low-grade alkoxyalkyl group, and low-grade alkenyl radical, an acyl group, the acylamino radical, an alkyl sulfonylamino radical, a hide ROKISHI imino alkyl group, an alkyloxy carbonylamino radical, alkyloxy carbonyloxy group, or the hetero aryl group that may be permuted. Moreover, two of R20, R21, and R22 can form the ring of the saturation which may become together and may contain the nitrogen atom, the sulfur atom, or the oxygen atom, or partial saturation. r means the integer of 0, or 1-8. The radical shown is meant.]
[Claim 3] The following general formula (3) The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology.
[Formula 22]
R1, R2, R3, R4, R5, and R6' have above semantics among [type.]
[Claim 4] The following general formula (4) The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology.
[Formula 23]
R1, R2, R3, R5, and R6' have above semantics among [type.]
[Claim 5] That R1, R2, R3, and R4 are the same, a nitrogen-containing heterocyclic compound given in any 1 term of claims 1-4 which are the hydrogen atom which is different from each other, a cyano group, a halogen atom, or a lower alkoxy group, or its salt permissible in pharmacology.
[Claim 6] A nitrogen-containing heterocyclic compound or its salt permissible in pharmacology given in any 1 term of claims 1-4 whose one of R1, R2, R3, and R4 is a cyano group, a chlorine atom, or a methoxy group.
[Claim 7] Said general formula (1) The nitrogen-containing heterocyclic compound according to claim 1 whose R2 it sets and is a cyano group, or its salt permissible in pharmacology.
[Claim 8] Said general formula (1) The nitrogen-containing heterocyclic compound according to claim 1 whose R2 it sets and is a halogen atom, or its salt permissible in pharmacology.
[Claim 9] Said general formula (1) The nitrogen-containing heterocyclic compound according to

claim 1 whose R2 it sets and is a chlorine atom, or its salt permissible in pharmacology.
[Claim 10] Said general formula (1) The nitrogen-containing heterocyclic compound according to claim 1 whose R2 it sets and is a lower alkoxy group, or its salt permissible in pharmacology.
[Claim 11] Said general formula (1) The nitrogen-containing heterocyclic compound according to claim 1 whose R2 it sets and is a methoxy group, or its salt permissible in pharmacology.
[Claim 12] It sets to said general formula (1), and R5 is a formula. - NR 11R12 (R11 and R12 mean among a formula same or hydrogen atom [which is different from each other], low-grade alkyl group, and hide ROKISHI alkyl group, amino alkyl group, carboxy alkyl group [that may be protected], alkyl carbamoyl group, 1, and 3-benzodioxolyl alkyl group or 1, and 4-benzodioxolyl alkyl group.) Furthermore, R11 R12 It becomes together with the nitrogen atom which they have combined, and the ring which may contain another nitrogen atom and the oxygen atom can be formed. Moreover, this ring may be permuted. The nitrogen-containing heterocyclic compound according to claim 1 which is the radical shown, or its salt permissible in pharmacology.
[Claim 13] Said general formula (1) It sets and R5 is a formula [** 24].
(— R60 means among a formula the hydroxyl group which may be protected, a cyano group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, the carboxyl group that may be protected, a hide ROKISHI alkyl group, a carboxy alkyl group, or a hetero aryl group.) — the nitrogen-containing heterocyclic compound according to claim 1 which is the radical shown, or its salt permissible in pharmacology.
[Claim 14] Said general formula (1) It sets and R5 is a formula [** 25].
(— R61 means among a formula the carboxyl group or hetero aryl group which may be protected.) — the nitrogen-containing heterocyclic compound according to claim 1 which is the radical shown, or its salt permissible in pharmacology.
[Claim 15] Said general formula (1) It sets and R5 is a formula [** 26].
(— the carboxyl group and u from which R61 may be protected mean 3 or 4 among a formula.) — the nitrogen-containing heterocyclic compound according to claim 1 which is the radical shown, or its salt permissible in pharmacology.
[Claim 16] Prevention / therapy agent of a disease with the effective phosphodiesterase inhibitory action which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 17] Prevention / therapy agent of a disease with the effective cyclic-GMP phosphodiesterase inhibitory action which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 18] Ischemic-heart-disease prevention / therapy agent which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 19] Angina pectoris prevention / therapy agent which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 20] Hypertension prevention / therapy agent which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 21] Cardiac insufficiency prevention / therapy agent which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 22] Asthmatic prevention / therapy agent which makes an active principle a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4.
[Claim 23] The physic constituent which consists of a nitrogen-containing heterocyclic compound or its salt permissible in pharmacology according to claim 1 to 4, and an excipient permitted in pharmacology.

[Translation done.]

Drawings are not displayable due to the volume of the data (more than 200 drawings).

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the nitrogen-containing heterocyclic compound which has the operation which was excellent as physic.
[0002]
[Description of the Prior Art] The angina pectoris which is one of the ischemic heart disease is known as many diseases to elderly people until now. As the therapy agent, although the nitric acid and the nitrous-acid compound, the calcium antagonist, beta-cutoff agent, etc. have been used, effectiveness is still inadequate for an angina pectoris therapy or progress prevention to myocardial infarction. Furthermore, the fall of an angina pectoris patient's age, complication of symptoms, etc. come to be seen according to increase of the stress accompanying change of life-form voice, and social complication etc., and it craves for the drugs superior to one new type recently.
[0003] The operation of a nitric acid and a nitrous-acid compound is considered that cyclic GMP in the cyclic nucleotide known as an intracellular second messenger (it omits Following cGMP) is involving among the drugs by which current use is carried out and which were mentioned previously. About cGMP, the relaxation operation of a blood vessel smooth muscle and a bronchial tube smooth muscle is known well. Although the action mechanism of these drugs is not necessarily clear, the activity of this cGMP activates the GUANI rate cyclase, and, generally it is considered the thing resulting from promoting cGMP composition. However, these drugs have low extent of bioavailability, and its reaction time is comparatively short. Moreover, producing resistance is reported and it has been a clinical top problem.
[0004] In view of such the actual condition, this invention person etc. started retrieval research that the drugs superior to one new type should be developed. That is, this invention persons came research in piles wholeheartedly over many years paying attention to cGMP phosphodiesterase (it abbreviates to cGMP-PDE below) inhibitory action about the compound which has these operations. The nitrogen-containing heterocyclic compound shown below as a result has these operations, and completed a header and this invention for it being effective in various ischemic heart disease etc.
[0005] As a quinazoline derivative useful as physic, although Patent Publication Heisei No. 502462 [two to] is mentioned, for example, this invention compound differs in structure and an operation.
[0006]
[Means for Solving the Problem] This invention is the following general formula (1). The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology is offered.
[0007]
[Formula 27]
[0008] They are the inside of [type, that R1, R2, R3, and R4 are the same or the low-grade alkyl group which may be permuted by the hydrogen atom which is different from each other, the

halogen atom, and the halogen atom and the cycloalkyl radical which may be permuted, a lower alkoxy group, a hide ROKISHI alkyl group, a nitro group, a cyano group, the acylamino radical, the carboxyl group that may be protected, and a formula [0009].
[Formula 28]
[0010] (-- R7 means a low-grade alkyl group among a formula, and n means the integer of 0, or 1-2.) -- the radical shown or formula [0011]
[Formula 29]
[0012] (The inside of a formula, that R45 and R46 are the same or the hydrogen atom which is different from each other, or a low-grade alkyl group is meant.) R45 and R46 It becomes together with the nitrogen atom which they have combined, and the ring which may contain another nitrogen atom and the oxygen atom can be formed. Moreover, this ring may be permuted. The radical shown is meant. Moreover, two may become together [of R1, R2, R3, and R4], and methylene dioxy, ethylene dioxy, or a phenyl ring may be formed.
[0013] R5 is the hydrogen atom, halogen atom, hydroxyl-group, hydrazino radical, low-grade alkyl group, and cycloalkyl radical which may be permuted, a lower alkoxy group, a low-grade alkenyl radical, the carboxy alkyl group that may be protected, the carboxy alkenyl radical which may be protected, a hide ROKISHI alkyl group, the carboxyl group which may be protected, and a formula [0014].
[Formula 30]
[0015] (-- R8 means a low-grade alkyl group among a formula, and m means the integer of 0, or 1-2.) -- the radical shown, the radical shown by formula-O-R9 (R9 means among a formula the hide ROKISHI alkyl group which may be protected, the carboxy alkyl group which may be protected, or the benzyl which may be permuted.), and formula [0016]
[Formula 31]
[0017] (-- R23 means a hydroxyl group, a low-grade alkyl group, a lower alkoxy group, a hide ROKISHI alkyl group, or a hide ROKISHI alkyloxy radical among a formula.) -- the radical shown -- The hetero aryl group which may be permuted, 1 which may be permuted, 3-benzodioxolyl radical, 1 which may be permuted, 4-benzodioxolyl radical, 1 which may be permuted, 3-benzodioxolyl alkyl group, The inside of 1 which may be permuted, 4-benzodioxolyl alkyl group, and a formula-C(R24) =X [type, and X are oxygen atom, sulfur atom, or formula =N-R10 (the inside of a formula and R10 mean a hydroxyl group, a cyano group, or the carboxy alkyloxy radical that may be protected.). the radical shown is meant -- R24 means a hydrogen atom or a low-grade alkyl group.] The radical come out of and shown, or formula - NR 11R12 (R11 and R12 mean among a formula same or hydrogen atom [which is different from each other], low-grade alkyl group, and hide ROKISHI alkyl group, amino alkyl group, carboxy alkyl group [that may be protected], alkyl carbamoyl group, carboxy alkyl carbamoyl group [which may be protected], heteroarylalkyl radical [which may be permuted], 1, and 3-benzodioxolyl alkyl group or 1, and 4-benzodioxolyl alkyl group.) Furthermore, R11 R12 It becomes together with the nitrogen atom which they have combined, and the ring which may contain another nitrogen atom and the oxygen atom can be formed. Moreover, this ring may be permuted. The radical shown is meant.
[0018] R6 is a hydrogen atom, a halogen atom, a hydroxyl group, the amino group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkenyl radical, 1, 3-benzodioxolyl alkyloxy radical, 1, 4-benzodioxolyl alkyloxy radical, the phenyl alkyloxy radical that may be permuted, and a formula [0019].
[Formula 32]
[0020] (R13 and R14 mean among a formula the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group.) Furthermore, R13 and R14 It may become together and methylene dioxy or ethylene dioxy may be formed. The radical shown, formula [0021]
[Formula 33]
[0022] (The inside of these formulas, that R15 and R16 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Further R15 R16 may become together and may form methylene dioxy or ethylene dioxy. A

piperidine-4-spiro-2'-dioxane-1-IRU radical, formula [0023]
[Formula 34]
[0024] (The inside of a formula, that R48 and R49 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Furthermore, R48 and R49 may become together and may form methylene dioxy or ethylene dioxy. Z means a sulfur atom or an oxygen atom. s means the integer of 0, or 1-8. The radical shown, formula [0025]
[Formula 35]
[0026] (— R50 means among a formula a hydroxyl group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, the carboxyl group that may be protected, a cyano group, a hide ROKISHI alkyl group, or a carboxy alkyl group.) — the radical shown and formula [0027]
[Formula 36]
[0028] R17 means among [type the hydrogen atom, low-grade alkyl group, acyl group, low-grade alkoxyalkyl group, and carboxy alkyl group which may be protected, or a hide ROKISHI alkyl group. Y is the radical shown by formula-(CH2) q- (q means the integer of 0, or 1-8 among a formula), or a formula [0029].
[Formula 37]
[0030] It comes out and the radical shown is meant. Furthermore, it is formula-(CH2) q. - In the radical shown, when q is the integer of 1-8, each carbon may have 1-2 substituents. R18 means a hydrogen atom, a hydroxyl group, the carboxyl group that may be protected, a cyano group, an acyl group, the hetero aryl group that may be permuted, or the cycloalkyl radical which may be permuted.] The radical come out of and shown, or a formula [0031]
[Formula 38]
[0032] (R19 means among a formula a hydrogen atom, a low-grade alkyl group, a low-grade alkoxyalkyl group, an acyl group, the carboxy alkyl group that may be protected, or a hide ROKISHI alkyl group.) R20, R21, and R22 mean a same or hydrogen atom [which is different from each other], halogen atom, hydroxyl-group, amino-group, nitro group, low-grade alkyl group, lower alkoxy group, low-grade alkoxyalkyl group, and low-grade alkenyl radical, an acyl group, the acylamino radical, an alkyl sulfonylamino radical, a hide ROKISHI imino alkyl group, an alkyloxy carbonylamino radical, alkyloxy carbonyloxy group, or the hetero aryl group that may be permuted. Moreover, two of R20, R21, and R22 can form the ring of the saturation which may become together and may contain the nitrogen atom, the sulfur atom, or the oxygen atom, or partial saturation. r means the integer of 0, or 1-8. The radical shown is meant.
[0033] R6 [however,] — the following type (i) (ii) — or (iii) The case where it is the radical shown is removed.
[0034]
[Formula 39]
[0035] (R19 has above semantics among a formula.) R25 means a halogen atom. R26 A lower alkoxy group is meant. R27 A hydrogen atom, a halogen atom, a nitro group, a low-grade alkyl group, or a lower alkoxy group is meant. R28 A hydrogen atom or a low-grade alkyl group is meant. y Mean the integer of ** 1-4. z Mean ** 1 or 2.]
Moreover, this invention is the following general formula (2). The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology is offered.
[0036]
[Formula 40]
[0037] R1, R2, R3, R4, and R5 have above semantics among [type.
[0038] R6' A hydrogen atom, a halogen atom, a hydroxyl group, the amino group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkenyl radical, 1, 3-benzodioxolyl alkyloxy radical, 1, 4-benzodioxolyl alkyloxy radical, the phenyl alkyloxy radical that may be permuted, formula
[0039]
[Formula 41]
[0040] (R13 and R14 mean among a formula the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group.) Furthermore, R13 and R14 It may become together and methylene dioxy or ethylene dioxy may be formed. The radical shown,

formula [0041]
[Formula 42]
[0042] (The inside of these formulas, that R15 and R16 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Further R15 R16 may become together and may form methylene dioxy or ethylene dioxy. A piperidine-4-spiro-2'-dioxane-1-IRU radical, formula [0043]
[Formula 43]
[0044] (The inside of a formula, that R48 and R49 are the same or the hydrogen atom which is different from each other, a low-grade alkyl group, or a lower alkoxy group is meant.) Furthermore, R48 and R49 may become together and may form methylene dioxy or ethylene dioxy. Z means a sulfur atom or an oxygen atom. s means the integer of 0, or 1-8. The radical shown, formula [0045]
[Formula 44]
[0046] (-- R50 means among a formula a hydroxyl group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, the carboxyl group that may be protected, a cyano group, a hide ROKISHI alkyl group, or a carboxy alkyl group.) -- the radical shown and formula [0047]
[Formula 45]
[0048] R17 means among [type the hydrogen atom, low-grade alkyl group, acyl group, low-grade alkoxyalkyl group, and carboxy alkyl group which may be protected, or a hide ROKISHI alkyl group. Y is the radical shown by formula-(CH2) q- (q means the integer of 0, or 1-8 among a formula), or a formula [0049].
[Formula 46]
[0050] It comes out and the radical shown is meant. Furthermore, it is formula-(CH2) q. - In the radical shown, when q is the integer of 1-8, each carbon may have 1-2 substituents. R18 means a hydrogen atom, a hydroxyl group, the carboxyl group that may be protected, a cyano group, an acyl group, the hetero aryl group that may be permuted, or the cycloalkyl radical which may be permuted.] The radical come out of and shown, or a formula [0051]
[Formula 47]
[0052] (R19 means among a formula a hydrogen atom, a low-grade alkyl group, a low-grade alkoxyalkyl group, an acyl group, the carboxy alkyl group that may be protected, or a hide ROKISHI alkyl group.) R20, R21, and R22 mean a same or hydrogen atom [which is different from each other], halogen atom, hydroxyl-group, amino-group, nitro group, low-grade alkyl group, lower alkoxy group, low-grade alkoxyalkyl group, and low-grade alkenyl radical, an acyl group, the acylamino radical, an alkyl sulfonylamino radical, a hide ROKISHI imino alkyl group, an alkyloxy carbonylamino radical, alkyloxy carbonyloxy group, or the hetero aryl group that may be permuted. Moreover, two of R20, R21, and R22 can form the ring of the saturation which may become together and may contain the nitrogen atom, the sulfur atom, or the oxygen atom, or partial saturation. r means the integer of 0, or 1-8. The radical shown is meant.]
Moreover, this invention is the following general formula (3). The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology is offered.
[0053]
[Formula 48]
[0054] R1, R2, R3, R4, R5, and R6' have above semantics among [type.]
Moreover, this invention is the following general formula (4). The nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology is offered.
[0055]
[Formula 49]
[0056] R1, R2, R3, R5, and R6' have above semantics among [type.]
Moreover, this invention is said general formula (1). - (4) Prevention [of a disease with especially effective cyclic-GMP phosphodiesterase inhibitory action] / therapy agent with the effective phosphodiesterase inhibitory action which makes an active principle the nitrogen-containing heterocyclic compound expressed or its salt permissible in pharmacology is offered. As such a disease, angina pectoris, hypertension, cardiac insufficiency, and asthma are mentioned to ischemic heart disease and a concrete target.

[0057] Furthermore, this invention offers the physic constituent which consists of said nitrogen-containing heterocyclic compound or its salt permissible in pharmacology, and an excipient permitted in pharmacology.
[0058] This invention compound (1) - (4) In the above-mentioned definition which can be set R1, R2, R3, R4, R5, R6, and R6', R7, R8, R11 and R12, R13, R14, R15, R16, and R17 and R19, R20, R21, R22, R23, R24, R27, R28, R45, R46, R48, R49, and R50 With the low-grade alkyl group seen by definition The straight chain of carbon numbers 1-8, or a branching-like alkyl group, for example, a methyl group, An ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical (amyl group), A neopentyl radical, a tert-pentyl radical, 2-methylbutyl radical, 3-methylbutyl radical, 1, 2-dimethyl propyl group, a hexyl group, an iso hexyl group, 1-methyl pentyl radical, 2-methyl pentyl radical, 3-methyl pentyl radical, 2, and 2-dimethyl butyl, 2, 3-dimethyl butyl, 3, and 3-dimethyl butyl, 2-ethyl butyl, 1, 1, a 2-trimethyl propyl group, 1 and 2, a 2-trimethyl propyl group, a 1-ethyl-1-methylpropyl radical, a 1-ethyl-2-methylpropyl radical, a heptyl radical, an octyl radical, etc. are meant. As a radical desirable [among these], a methyl group, an ethyl group, a propyl group, an isopropyl group, etc. can be mentioned. As a desirable radical, a methyl group and an ethyl group can be mentioned among these especially.
[0059] Moreover, for these low-grade alkyl groups, the carbon atom of an end is a sulfonic group (-SO3H). Formula - ONO2 You may permute by the radical shown. Furthermore, a sulfonic group is formula-SO3Na and formula-SO3K. A salt like the radical shown may be formed.
[0060] The low-grade alkyl group which may be permuted by the halogen atom seen by the definition of R1, R2, R3, and R4 means the low-grade alkyl group by which the hydrogen atom of the above-mentioned low-grade alkyl group may be permuted by one piece or the two or more piece halogen atom.
[0061] R1, R2, R3, R4, R5, R6, R6', R13, and R14, R15, R16, R20, R21, R22 and R23, R26, R27, R48, R49, and R50 With the lower alkoxy group seen in a definition The straight chain of carbon numbers 1-8, or a branching-like alkoxy group, for example, a methoxy group, An ethoxy radical, n-propoxy group, an isopropoxy group, an n-butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, 2-methyl butoxy radical, 2, 3-dimethyl butoxy radical, a hexyloxy radical, etc. are meant. A methoxy group, an ethoxy radical, etc. can be mentioned as a radical desirable [among these].
[0062] R5, R6, R6', R20, R21, and R22 With the low-grade alkenyl radical seen by definition, the radical guided from the above-mentioned low-grade alkyl group, for example, ethylene, a propylene radical, a butylene radical, an isobutylene radical, etc. can be mentioned.
[0063] R1, R2, R3, R4, R5, R11, R12, R17, R19, R23, and R50 The hide ROKISHI alkyl group seen by definition means the radical guided from the above-mentioned low-grade alkyl group.
[0064] In the definition of R9, with the hide ROKISHI alkyl group which may be protected The hydroxyl group in hide ROKISHI alkyl For example, the case where it is the radical protected by the nitro group, The case where it is the radical protected by the low-grade alkyl group hung up over the above, such as a methyl group and an ethyl group, The case where it is the radical protected by the radical considered to have cGMP-PDE inhibition activity when it is the radical protected by acyl groups, such as an acetyl group, a propionyl radical, a BUCHIROIRU radical, a pivaloyl radical, and a nicotinoyl group, is mentioned. Moreover, these protective groups shift, or remain as it is and demonstrate drug effect in the living body.
[0065] R17, R18, R19, R20, and R21 and R22 With the acyl group seen by definition, hetero aroyl radicals, such as aroyl radicals, such as low-grade alkanoyl radicals, such as aliphatic series, aromatic series and the acyl group guided from heterocycle, for example, a formyl group, an acetyl group, a propionyl radical, a butyryl radical, a valeryl radical, an iso valeryl radical, and a pivaloyl radical, benzoyl, a toluoyl radical, and a naphthoyl radical a furoyl radical, a nicotinoyl group, and an isonicotinoyl group, etc. can be mentioned. A formyl group, an acetyl group, benzoyl, etc. can be mentioned preferably among these.
[0066] R1, R2, R3, R4, R5, R18, and R50 In a definition as a protective group of a carboxyl group Low-grade alkyl group;p-methoxybenzyl, such as methyl, ethyl, and t-butyl, p-nitrobenzyl, 3, 4-dimethoxy benzyl, diphenyl methyl, The low-grade alkyl group permuted by the phenyl group

which may have substituents, such as trityl and phenethyl; 2, 2, and 2-trichloroethyl, Halogenation low-grade alkyl groups, such as 2-iodine ethyl; Pivaloyloxymethyl, Acetoxy methyl, propionyl oxymethyl, butyryl oxymethyl, Valeryl oxymethyl, 1-acetoxy ethyl, 2-acetoxy ethyl, Low-grade alkanoloxy low-grade alkyl groups, such as 1-pivaloyloxy ethyl and 2-pivaloyloxy ethyl; PARUMITO yloxy ethyl, High-class alkanoloxy low-grade alkyl groups, such as heptadeca noil oxymethyl and 1-PARUMITO yloxy ethyl; Methoxycarbonyl oxymethyl, Low-grade alkoxy carbonyloxy low-grade alkyl groups, such as 1-BUTOKI carbonyloxy ethyl and 1-(isopropoxycarbonyloxy) ethyl; Carboxymethyl, carboxies, such as 2-carboxy ethyl, -- low-grade -- heterocycle radical [, such as alkyl group;3-free-wheel-plate RIJIRU]; -- 4-glycyl oxy-benzoyloxy methyl -- 4-[N- The benzoyloxy low-grade alkyl group which may have substituents, such as glycyl oxy-] benzoyl oxymethyl; (5-methyl-2-oxo-- 1, 3-JIOKISOREN-4-IRU) Low-grade (permutation JIOKISOREN) alkyl group [, such as methyl,]; (T-butoxycarbonyl) Cycloalkyloxy carbonyloxy low-grade alkyl groups, such as cycloalkyl permutation low-grade alkanoloxy low-grade alkyl groups, such as 1-cyclohexyl acetyloxy ethyl, and 1-cyclohexyloxycarbonyloxyethyl, etc. are mentioned.

[0067] Furthermore, although you may be various acid amides, as long as it is the protective group which decomposes in the living body and can turn into a carboxyl group, what kind of thing may be used. These protective groups shift, or remain as it is and demonstrate drug effect in the living body.

[0068] R1, R2, R3, R4, R5, and R18 Although the cycloalkyl radical which is seen by definition and which may be permuted means the thing of carbon numbers 3-8, it is the thing of carbon numbers 3-6 preferably.

[0069] R5, R18, R20, and R21 And R22 In the hetero aryl group which is seen by definition and which may be permuted, hetero aryl means the monocycle radical or condensation heterocycle radical of five to 7 membered-ring which contained 1-2 oxygen atoms, the nitrogen atom, or the sulfur atom as a hetero atom, for example, a furil radical, a pyridyl radical, a thienyl group, an imidazolyl radical, a chinae-cortex ZORIRU radical, a benzoimidazolyl radical, etc. are mentioned.

[0070] R11 and R12 In the heteroarylalkyl radical which is seen by definition and which may be permuted, it has the semantics as the above-mentioned hetero aryl group with the same hetero aryl. Moreover, it has the semantics as the above-mentioned low-grade alkyl group with the same alkyl group in this case.

[0071] R11 and R12 -- and -- R45 and R46 If "it can become together with the nitrogen atom which R12 (46) has combined with R11 (45), and the ring which may contain another nitrogen atom and the oxygen atom can be formed" gives an example concretely, a piperidino radical, a piperazino radical, a morpholino radical, etc. are meant. [which is looked at by definition] as the substituent which can furthermore be permuted by this ring -- low-grade alkyl group [, such as halogen atom; methyls, such as a hydroxyl-group; chlorine atom, a fluorine atom, a bromine atom, and an iodine atom, ethyl, and t-butyl,]; -- hetero aryl groups, such as a carboxyl group; hydroxyalkyl radical; carboxy alkyl group; tetrazolyl group by which lower alkoxy group; cyano group; protection of methoxy and ethoxy **t-butoxy etc. may be done, etc. can be mentioned. It can have these substituents to the 1-2 above-mentioned rings.

[0072] Moreover, R5, R18, R20, R21, "the hetero aryl group which may be permuted" looked at by the definition of R22, R6 and R6' "The phenyl alkyloxy radical which may be permuted" seen by definition, "The definition of R5 sees. 1, 3-bends dioxolyl radical which may be permuted, 1 which may be permuted, 4-BENZUJI oxyl radical, 1 which may be permuted, 3-bends dioxolyl alkyl group, 1 which may be permuted, 4-benzdioxylalkyl group", "the benzyl which may be permuted" seen by the definition of R9, R11 and R12 In "the heteroarylalkyl radical which may be permuted" seen by definition as a substituent For example, halogen atoms, such as a hydroxyl-group; nitro group; chlorine atom, a fluorine atom, a bromine atom, and an iodine atom; Methyl, Low-grade alkyl groups, such as ethyl and t-butyl; the carboxyl group; hydroxyalkyl radical; carboxy alkyl group; tetrazolyl group by which lower alkoxy group; protection of methoxy and ethoxy **t-butoxy etc. may be done can be mentioned.

[0073] Further It sets "for each carbon to have 1-2 substituents in the radical shown by formula-(CH2) q-, when q is the integer of 1-8", and has the semantics as the above-mentioned

substituent with the same substituent. [which is found by the definition of Y]
[0074] R1, R2, R3, R4, R20, and R21 and R22 Although the radical to which the above-mentioned acyl group combined the acylamino radical with the nitrogen atom of the amino group, i.e., a mono-permutation-acylamino radical, and the acylamino radical of a JI permutation are meant in a definition, the acylamino radical of a mono-permutation is desirable.
[0075] R1, R2, R3, R4, R5, R6, R6', R20, R21, R22, R25, R27, and R50 In a definition, a halogen atom means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, etc.
[0076] R5, R9, R10, R11, R12 and R17, and R19 The carboxy alkyl group which may be protected in the definition means the carboxy alkyl group which may be protected by the protective group of the above-mentioned carboxyl group. Moreover, the carboxy group in this carboxy alkyl shall be combined with one 1-2 carbon atoms of the above-mentioned low-grade alkyl groups.
[0077] The carboxy alkenyl radical which may be protected in the definition of R5 means the carboxy alkenyl radical which may be protected by the protective group of the above-mentioned carboxyl group. Moreover, the carboxyl group in this carboxy alkenyl shall be combined with one 1-2 carbon atoms of the above-mentioned low-grade alkenyl radicals.
[0078] R17, R19, R20, and R21 and R22 In a definition, the radical guided from the above-mentioned low-grade alkyl group, for example, a methoxymethyl radical, a methoxy ethyl group, methoxy butyl, an ethoxyethyl radical, etc. can be mentioned with a low-grade alkoxyalkyl group.
[0079] R11 and R12 In a definition, an amino alkyl group means the radical which the amino group has permuted by one which constitutes the above-mentioned low-grade alkyl group of carbon atoms. R11 and R12 In a definition, an alkyl carbamoyl group means the radical guided from the above-mentioned low-grade alkyl group.
[0080] R11 and R12 The carboxy alkyl carbamoyl group which is seen by definition and which may be protected means what the carboxy which may be protected by one carbon of the alkyls of the above-mentioned alkyl carbamoyl group has combined.
[0081] R20, and R21 and R22 In a definition, an alkyl sulfonylamino radical means the radical guided from the above-mentioned low-grade alkyl group. R20, and R21 and R22 The hydroxyiminoalkyl group seen by definition means what the hydroxyimino group combined with one carbon atom of the above-mentioned low-grade alkyl groups.
[0082] R20, and R21 and R22 Although the alkyloxy carbonyl guided from the above-mentioned low-grade alkyl group says monochrome or the thing which carried out the JI permutation to the nitrogen atom of the amino group, the alkyloxy carbonylamino radical of a mono-permutation of the alkyloxy carbonylamino radical seen by definition is more desirable.
[0083] R20, and R21 and R22 The alkyloxy carbonyloxy group seen by definition means the radical which the alkyloxy carbonyl guided from the above-mentioned low-grade alkyl group has combined with the oxygen atom. The hide ROKISHI alkyloxy radical seen by the definition of R23 means the radical guided from the above-mentioned hide ROKISHI alkyl group.
[0084] In this invention, a salt with amino acid, such as organic-acid salts, such as inorganic-acid salts, for example, acetate, such as a hydrochloride, hydrobromate, a sulfate, and phosphate, a maleate, a tartrate, a methansulfonic acid salt, a benzenesulfonic acid salt, and a toluenesulfonic acid salt, or an arginine, an aspartic acid, and glutamic acid, etc. can be mentioned with a salt permissible in pharmacology. Furthermore, it is included by the salt which may take metal salts, such as Na, K, calcium, and Mg, depending on a compound, and can be permitted like pharmacology of this invention.
[0085] Moreover, although this invention compound group can take geometrical isomers, such as a cis- object and a transformer object, and various isomers, such as optical isomers, such as d bodies and l etc. bodies, with a class, combination, etc. of a substituent, it cannot be overemphasized that any isomer is included by this invention compound group.
[0086] The typical manufacture approach of this invention compound is shown below. Although the compound which mainly has a quinazoline frame below is explained, when ring parts are other frames, it can apply similarly.
[0087] Manufacture approach 1 general formula (1) It can set and can manufacture also by the following approaches at the time of the radical chosen from the radicals which R5 combines with a hydrogen atom, a halogen atom, and a quinazoline frame by the direct carbon atom.

[0088]
[Formula 50]
[0089] (R5a shows the radical chosen from the radical combined with a hydrogen atom, a halogen atom, and said quinazoline frame by the direct carbon atom in said R5 among a series of formulas.) R1, R2, R3, and R4 have above semantics.
Namely, general formula (5) It is a general formula (6) by making phosphorus oxychloride act on the quinazoline derivative expressed, or making the bottom phosphorus oxychloride of phosphorus-pentachloride existence act, and heating. It is the reaction which obtains the quinazoline derivative expressed.
[0090] Manufacture approach 2 general formula (1) It sets and R5 is a hydrogen atom, a halogen atom, and a formula [0091].
[Formula 51]
[0092] It is radical and formula-O-R9 (among a formula) shown by (R8 and m have above semantics among a formula). R9 has above semantics. The radical shown, the hetero aryl group which may be permuted, the radical combined with a ring part by the direct carbon atom for example, a low-grade alkyl group and the carboxyl group which may be protected — 1 which may be permuted, 3-benzodioxolyl radical, 1 which may be permuted, 4-benzodioxolyl radical, They are 1 which may be permuted, 3-benzodioxolyl alkyl group and 1 which may be permuted, and the radical chosen from 4-benzoJIOKI sill alkyl group. It can obtain by the following approaches at the time of the radical chosen from from while R6 removed the hydrogen atom, the halogen atom, and the low-grade alkyl group from said definition of R6.
[0093]
[Formula 52]
[0094] R1, R2, R3, and R4 have above semantics among the formula of a [single string. R5b A hydrogen atom, a halogen atom, formula [0095]
[Formula 53]
[0096] (— R8 and m have above semantics among a formula.) — the radical shown and the radical shown by formula-O-R9 (the inside R9 of a formula has above semantics.) — The hetero aryl group which may be permuted, and the radical combined with a ring part by the direct carbon atom for example, a low-grade alkyl group and the carboxyl group which may be protected — 1 which may be permuted, 3-benzodioxolyl radical, 1 which may be permuted, 4-benzodioxolyl radical, 1 which may be permuted, 3-benzodioxolyl alkyl group and 1 which may be permuted, and the radical chosen from 4-benzodioxolyl alkyl groups are meant. R6a The radical chosen from from while removing the hydrogen atom, the halogen atom, and the low-grade alkyl group from said definition of R6 is meant. E means a leaving group.]
Namely, general formula (7) The quinazoline derivative and general formula (9) which are expressed By carrying out condensation of the compound expressed, it is the purpose compound (8). It is the approach of obtaining.
[0097] Inside of a formula A halogen atom and an alkoxy group are mentioned as a leaving group expressed with E. As occasion demands, this approach can recommend a reaction under existence of a base. As a base, alkoxides, such as inorganic bases, such as organic bases, such as triethylamine, a pyridine, and diisopropyl ethylamine, a sodium carbonate, potassium carbonate, a sodium hydrogencarbonate, a sodium hydroxide, and sodium hydride, sodium methoxide, and potassium t-butoxide, are mentioned.
[0098] Although all the solvents that do not participate in a reaction can be used as a reaction solvent, ethanol, isopropyl alcohol, a tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, etc. can be mentioned as an example. Moreover, this approach can recommend a reaction, even if a reaction solvent does not exist by the case. -20 degrees C - 300 degree C of reaction temperature is desirable.
[0099] Manufacture approach 3 general formula (1) It sets, and when it is the radical chosen from from while removing the radical which R5 combines with a hydrogen atom, a halogen atom, and a quinazoline frame by the direct carbon atom from the definition of Rsaid 5 and is the radical chosen from from while R6 removed the halogen atom from said definition of R6, it can manufacture by the following approaches.

[0100]
[Formula 54]
[0101] (R1, R2, R3, and R4 have above semantics among a series of formulas.) R5c The radical chosen from from while removing the radical combined with a hydrogen atom, a halogen atom, and a quinazoline frame by the direct carbon atom from the definition of Rsaid 5 is meant. R6b The radical chosen from from while removing the halogen atom from said definition of R6 is meant. F means a leaving group.
Namely, the compound and general formula (12) which are expressed with a general formula (10) By carrying out condensation of the compound expressed, it is the approach of obtaining the purpose compound (11).
[0102] Inside of a formula As a leaving group expressed with F, a halogen atom, an alkylthio group, etc. can be mentioned as an example.
[0103] This approach can recommend a reaction under existence of a base as occasion demands. As a base, alkoxides, such as inorganic bases, such as organic bases, such as triethylamine, a pyridine, and diisopropyl ethylamine, a sodium carbonate, potassium carbonate, a sodium hydrogencarbonate, a sodium hydroxide, and sodium hydride, sodium methoxide, and potassium t-butoxide, can be mentioned.
[0104] Although all the solvents that do not participate in a reaction can be used as a reaction solvent, if an example is given, ethanol, isopropanol, a tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, etc. can be mentioned. 0 degree C - 300 degree C of reaction temperature is desirable.
[0105] Manufacture approach 4 general formula (1) It sets and R5 is a formula [0106].
[Formula 55]
[0107] (-- R24 means a hydrogen atom and a low-grade alkyl group among a formula.) -- at the time of the radical shown, it can manufacture also by the following approaches.
[0108]
[Formula 56]
[0109] (R1, R2, R3, R4, and R6 have above semantics among a series of formulas.) R24 and R29 The same, the hydrogen atom which is different from each other, or a low-grade alkyl group is meant.
Namely, general formula (13) It is the approach of oxidizing the compound expressed via an alcoholic object (15) with a usual reducing agent and a usual nucleophilic reagent depending on direct or the case, and obtaining the purpose compound (14).
[0110] As a reducing agent, a lithium aluminum hydride, a sodium borohydride, a diisobutyl aluminum hydride, etc. can be mentioned.
[0111] As a nucleophilic reagent, low-grade alkyl metals, such as methyl lithium and methyl magnesium bromide, etc. can be mentioned.
[0112] A potassium-dichromate-sulfuric acid, dimethyl sulfoxide-oxalyl chloride, etc. are mentioned as an oxidizing agent at the time of going via alcohol.
[0113] All the solvents that do not participate in a reaction can be used as a reaction solvent. Reaction temperature is the reflux temperature of 0 degree C to a solvent.
[0114] Manufacture approach 5 general formula (1) It sets and R5 is a formula [0115].
[Formula 57]
[0116] (-- the inside of a formula, and R10 and R24 have above semantics.) -- at the time of the radical shown, it can manufacture also by the following approaches.
[0117]
[Formula 58]
[0118] (The inside of a series of formulas, and R1, R2, R3, R4, R6 and R10 [R24 has above semantics.] It reaches)
Namely, general formula (14) The compound and hydroxy amine which are expressed are made to react and it is a general formula. (16) It is the approach of obtaining the compound expressed.
[0119] All the solvents that do not participate in a reaction can be used for a reaction solvent. Reaction temperature is the reflux temperature of 0 degree C to a solvent.
[0120] Manufacture approach 6 general formula (1) It sets and R5 is a formula [0121].

[Formula 59]
[0122] (The inside of a formula and R24 have above semantics.) R30 means a hydrogen atom or a low-grade alkyl group. R31 means a hydrogen atom, a low-grade alkyl group, the carboxyl group that may be protected, and the carboxy alkyl group which may be protected. It can manufacture also by the following approaches at the time of the radical shown.
[0123]
[Formula 60]
[0124] (R1, R2, R3, R4, R6, R24, and R30 and R31 have above semantics among a series of formulas.) Ph means a phenyl group.
That is, it is the approach of obtaining the compound which the compound expressed with a general formula (14) is made reacting according to the compound and Wittig reaction which are expressed with a general formula (18) or a general formula (19), and is expressed with a general formula (17).
[0125] All the solvents that do not participate in a reaction can be used for a reaction solvent. Reaction temperature is from 0 degree C to the reflux temperature of a solvent.
[0126] Manufacture approach 7 general formula (1) It sets and R5 is a formula [0127].
[Formula 61]
[0128] (— the inside of a formula, R24, and R30 and R31 have above semantics.) — when shown, it can manufacture also by the following approaches.
[0129]
[Formula 62]
[0130] (The inside of a series of formulas, R1, R2, R3, R4 and R6, and R24 and R30 [R31 has above semantics.] It reaches)
That is, it is the approach of obtaining the purpose compound (20) by returning the compound expressed with the general formula (17) obtained by the manufacture approach 6.
[0131] Reduction is performed by the catalytic reduction by a usual approach, for example, palladium-carbon, or a usual platinum catalyst etc. All the solvents with which a reaction solvent does not participate in a reaction are used.
[0132] Manufacture approach 8 general formula (1) It sets and R6 is a formula [0133].
[Formula 63]
[0134] (— the inside of a formula, R19, R20 and R21, and r have above semantics.) — at the time of the radical shown, it can manufacture also by the following approaches.
[0135]
[Formula 64]
[0136] (In a series of formulas, R1, R2, R3, R4, R5, R19, R20 and R21, and r have above semantics.)
That is, it is the approach of returning the compound expressed with a general formula (21), and obtaining the purpose compound (22).
[0137] Reduction is performed by the reduction using the catalytic reduction by a usual approach, for example, palladium-carbon, or a usual platinum catalyst or iron, and tin etc. All the solvents that do not participate in a reaction can be used for a reaction solvent.
[0138] Manufacture approach 9 general formula (1) It can set and can manufacture by the following approaches at the time of the radical R5 is indicated to be by formula-O-R9' (R9' means among a formula the carboxy alkyl group which may be protected.).
[0139]
[Formula 65]
[0140] (In a series of formulas, R1, R2, R3, R4, and R6 have above semantics.) m means the integer of 0, or 1-2.
That is, it is the reaction which obtains the compound which oxidizes the compound expressed with a general formula (23) by the usual approach, and is expressed with a general formula (24).
[0141] Although all things can be used if it is the oxidizer usually used as an oxidizer, hexavalent chromium, dimethyl sulfoxide, oxalyl chloride, etc. can be mentioned, for example.
[0142] All the solvents that do not participate in a reaction can be used as a reaction solvent. Reaction temperature is from 0 degree C to the reflux temperature of a solvent.

[0143]
[Formula 66]
[0144] (In a series of formulas, R1, R2, R3, R4, R6, and m have above semantics.) R32, R33, and R34 The same, the hydrogen atom which is different from each other, or a low-grade alkyl group is meant.
That is, it is the approach of obtaining the compound which a Wittig reagent (25) or (25)' is made reacting to the compound (24) obtained at the first process, and is expressed with a general formula (26).
[0145] All the things that do not participate in a reaction can be used for a reaction solvent. Reaction temperature is from 0 degree C to the reflux temperature of a solvent.
[0146]
[Formula 67]
[0147] (In a series of formulas, R1, R2, R3, R4, R6, R33, R34, and m have above semantics.) That is, it is the approach of returning the compound (26) obtained at the second process, and obtaining the purpose compound (27). Although reduction is performed by the usual approach, the catalytic reduction by palladium-carbon or the platinum catalyst etc. is mentioned, for example.
[0148] Manufacture approach 10 general formula (1) It sets and R6 is a formula [0149].
[Formula 68]
[0150] (The inside of a formula, R19, R20 and R21, and r have above semantics.) R35 means an acyl group, a low-grade alkyl sulfonyl group, and a low-grade alkyloxy carbonyl group. At the time of the radical shown, it can manufacture also by the following approaches.
[0151]
[Formula 69]
[0152] (In a series of formulas, R1, R2, R3, R4, R5, R19, R20 and R21, R35, and r have above semantics.)
That is, it is the approach of obtaining the purpose compound (28) under base existence acylation according the compound expressed with the general formula (22) obtained by the manufacture approach 8 to the usual approach, sulfonyl-izing, or by carrying out an alkoxy carbonylation.
[0153] As an acylating agent, all acylating agents usually used, such as condensing agents, such as carboxylic-acid activators, such as an acid chloride, an acid anhydride, and a mixed acid anhydride, and dicyclohexylcarbodiimide, are used.
[0154] Although all the sulfonyl-ized agents usually used are usable as a sulfonyl-ized agent, if an example is given, they will be low-grade alkyl sulfonyl chloride, a low-grade alkyl sulfonic-acid anhydride, etc.
[0155] As an alkoxy carbonylation agent, all the alkoxy carbonylation agents usually used, for example, low-grade alkyloxy carbonyl chloride, low-grade ARUKIRUPIRO carbonate, etc. can be mentioned.
[0156] As a base, although all bases are usable, inorganic bases, such as organic bases, such as a pyridine and triethylamine, a sodium carbonate, potassium carbonate, a sodium hydroxide, and sodium hydride, etc. can be mentioned, for example.
[0157] Manufacture approach 11 general formula (1) - (4) Set and the radical chosen from the thing except the radical which R5 combines with a ring part by the direct carbon atom among said definitions of R5 is meant. It is general formula (1) - (4) at the time of the radical chosen from the thing except the radical which R6 combines with a ring part by the direct carbon atom among said definitions of R6. The compound expressed can be manufactured also by the following approaches. In addition, the case where the ring part forms the quinazoline frame in below as an above representative is shown.
[0158]
[Formula 70]
[0159] (R1, R2, R3, and R4 have above semantics among a series of formulas.) R5d Although the radical combined with a ring part by the direct carbon atom among said definitions of R5 was removed, the radical chosen from inside is meant. X means a halogen atom.

That is, it is a condensation reaction by the usual approach.
[0160] Although it is desirable to use ether system solvents, such as alcoholic solvent, such as isopropyl alcohol, and a tetrahydrofuran, dimethylformamide, etc. as for a reaction solvent, all the organic solvents that do not participate in a reaction can be used.
[0161] R5d When combining with a ring part by the nitrogen atom, under tertiary amine existence, such as triethylamine, heating reflux is carried out and it generates. It is desirable to recommend a reaction, removing HCl. Moreover, R5d When combining with a ring part by the oxygen atom or the sulfur atom, it is desirable to carry out heating reflux under alkali existence, such as a sodium hydroxide and a sodium carbonate, and to advance a reaction.
[0162]
[Formula 71]
[0163] (R1, R2, R3, R4, R5d, and X have above semantics among a series of formulas.) R6c The radical chosen from the thing except the radical combined with a ring part by the direct carbon atom is meant out of said definition of R6.
It is a general formula with the usual approach about the compound (30) obtained at the first process. It is the reaction which carries out condensation to the compound shown by R6 c-H.
[0164] Although it is desirable to use ether system solvents, such as alcoholic solvent, such as isopropyl alcohol, and a tetrahydrofuran, dimethylformamide, etc. as for a reaction solvent, all the organic solvents that do not participate in a reaction can be used.
[0165] R6c When combining with a ring part by the nitrogen atom, they are inorganic bases, such as organic bases, such as triethylamine, a pyridine, and ethyl diisopropylamine, a sodium carbonate, potassium carbonate, a sodium hydrogencarbonate, sodium hydride, and a sodium hydroxide, sodium methoxide, and a potassium. It is desirable to carry out heating reflux under existence of alkoxides, such as t-butoxide, etc., and to recommend a reaction. Moreover, R6c When combining with a ring part by the oxygen atom or the sulfur atom, it is desirable to carry out heating reflux under alkali existence, such as a sodium hydroxide and a sodium carbonate, and to advance a reaction.
[0166] Manufacture approach 12 general formula (3) The compound shown is following general formula (34): [0167].
[Formula 72]
[0168] It comes out, and when it is the compound shown, this compound can be manufactured also by the following approaches.
[0169]
[Formula 73]
[0170] (R1, R2, R3, R4, and R5 have above semantics among a series of formulas.) R6d The radical chosen from the radical combined with a ring part by the direct carbon atom is meant during said definition of R6.
That is, it is the reaction which piperonyl chloride (33) is made to react with the benzimidazole derivative shown by the general formula (32), and obtains the purpose compound by the usual approach under alkali existence.
[0171] As alkali, a sodium iodide etc. is desirable. Although all the solvents that do not participate in a reaction are usable as a reaction solvent, polar solvents, such as dimethylformamide, can be mentioned preferably. About 60 to 100 degree C is desirable especially desirable, and reaction temperature is about 70-80 degrees C.
[0172] A manufacture approach 13 this invention compound can be manufactured also by the following approaches.
[0173]
[Formula 74]
[0174] (R1, R2, R3, and R4 have above semantics among a series of formulas.) R6e Although the radical combined with a ring part by the direct carbon atom was removed from said definition of R6, the radical chosen from inside is meant. Q and Q' means a halogen atom.
The first process is a condensation reaction by the usual approach.
[0175] R6e When combining with a ring part by the nitrogen atom, they are inorganic bases, such as organic bases, such as triethylamine, a pyridine, and diisopropyl ethylamine, a sodium

carbonate, potassium carbonate, a sodium hydrogencarbonate, a sodium hydroxide, and sodium hydride, sodium methoxide, and a potassium. It is desirable to carry out heating reflux under existence of alkoxides, such as t-butoxide, and to recommend a reaction. Moreover, R6e When combining with a ring part by the oxygen atom or the sulfur atom, it is desirable to carry out heating reflux under inorganic base existence, such as a sodium hydroxide and a sodium carbonate, and to advance a reaction.
[0176] Although all the solvents that do not participate in a reaction can be used as a reaction solvent, ether system solvents, such as alcoholic solvent, such as ethanol and isopropyl alcohol, and a tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, etc. can be mentioned as an example. Moreover, this approach can recommend a reaction, even if a reaction solvent does not exist by the case.
[0177]
[Formula 75]
[0178] (R1, R2, R3, R4, R6e, and Q' have above semantics among a series of formulas.) R5e means the radical chosen from the thing except the radical combined with a ring part by the direct carbon atom out of said definition of R5.
That is, it is the approach of obtaining the purpose compound, by carrying out condensation of the compound obtained at the first process, and the compound expressed with general formula R5 e-H.
[0179] This approach can recommend a reaction under existence of a base as occasion demands. As a base, they are inorganic bases, such as organic bases, such as triethylamine, a pyridine, and diisopropyl ethylamine, a sodium carbonate, potassium carbonate, a sodium hydrogencarbonate, a sodium hydroxide, and sodium hydride, sodium methoxide, and a potassium. Alkoxides, such as t-butoxide, can be mentioned.
[0180] Although all the solvents that do not participate in a reaction can be used as a reaction solvent, if an example is given, ether system solvents, such as alcoholic solvent, such as ethanol and isopropanol, and a tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, etc. can be mentioned.
[0181] 0 degree C - 300 degree C of reaction temperature is desirable. R5e In the case of the radical combined with a ring part by the nitrogen atom, it is desirable to carry out heating reflux under tertiary amine existence, such as triethylamine, and to recommend a reaction. Moreover, R5e In the case of the radical combined with a ring part by the oxygen atom or the sulfur atom, it is desirable to carry out heating reflux under alkali existence, such as a sodium hydroxide and a sodium carbonate, and to advance a reaction.
[0182] The compound obtained by the manufacture approaches 1-13 above can build a salt by the approach usually performed, such as adding a sodium hydroxide, a potassium hydroxide, methansulfonic acid Krol, etc.
[0183] Next, the manufacture approach of the raw material compound used by the manufacture approach is shown.
a ring part is a quinazoline ring among the starting material used by the manufacture approach A manufacture approach 13 — the compound whose Q and Q' is a chlorine atom can be manufactured also by the following approaches.
[0184]
[Formula 76]
[0185] (R1, R2, R3, and R4 have above semantics among a series of formulas.) X' means the radical of either a hydroxyl group, an alkoxy group or the amino group.
Namely, compound (a) A ring closure is carried out by the approach usually performed, and it is a compound (b). It is the purpose compound (c) by obtaining and chlorinating by the after that usual approach. It is the approach of acquiring.
[0186] The first process is a ring closure reaction. A urea and compound (a) It is made to react and is a compound (b). It is the process to acquire. The reaction temperature in this case is abbreviation. 170 to 190 degree C is desirable, and although a reaction solvent can use all organic solvents if it does not participate in a reaction, it can mention N-methyl pyrrolidone etc. preferably. Moreover, this process can advance [solvent / non-] a reaction.

[0187] Furthermore, when X' is an amino group, after making it cyclize by carbonyldiimidazole etc. or making it urethane by chloroformate etc., it can obtain also by making it cyclize under an acid or a basic condition.
[0188] The second process is a chlorination reaction. Although this process can be performed by the approach usually performed, it can mention the approach of carrying out heating-under stirring reflux with a phosphorus pentachloride and phosphorus oxychloride, or phosphorus oxychloride, and chlorinating etc., for example.
[0189] Starting material used by the manufacture approach B manufacture approach 1 (5) It can manufacture by the following approaches.
[0190]
[Formula 77]
[0191] (The inside of a series of formulas, and R1, R2, R3 and R4 have above semantics.) R5f The radical chosen from the radicals combined with a halogen atom and a ring part by the carbon atom is meant during said definition of R5.
That is, it is the reaction which acquires an amide object by the approach usual at the first process, and carries out a ring closure under existence of an acid or a base at the second process.
[0192] Amide object (e) Although it can obtain by the usual approach, they are the bottom of base existence, and a compound (d), for example. R5 f-COCl It can obtain by making it react with acylating agents, such as an acid chloride shown. As a base, organic bases, such as tertiary amine, such as triethylamine, and a pyridine, can be mentioned preferably.
[0193] Specifically as an acylating agent, acid chlorides, such as benzoyl chloride, acetyl chloride, ethyl oxalyl chloride, and benzyloxy acetyl chloride, etc. can be mentioned. About 0 degree C - 30 degrees C of reaction temperature are desirable.
[0194] Compound obtained at the first process in the second process (e) It is a compound (f) by carrying out heating reflux under an acid or base existence. It is obtained.
[0195] An acetic anhydride etc. can be mentioned as an acid. A sodium hydroxide etc. can be mentioned as a base.
[0196] It sets to the manufacture approach C manufacture approach 1, and is R5a. When it is a hydrogen atom, it is starting material (5). It can manufacture also by the following approaches.
[0197]
[Formula 78]
[0198] (The inside of a series of formulas, and R1, R2, R3 and R4 have above semantics.) X" means a hydroxyl group or a lower alkoxy group.
That is, it is a ring closure reaction by the usual approach.
[0199] For example, raw material compound (g) It is the purpose compound (h) by carrying out heating reflux with a formamide, carrying out condensation or heating with a formic acid. It is compoundable.
[0200]
[Effect of the Invention] Next, in order to explain the effectiveness of this invention compound in full detail, the example of an experiment is hung up.
[0201] enzyme inhibition operation 1. using cGMP-PDE obtained from the example Buta main artery of an experiment the enzyme activity of cGMP-PDE prepared from the experiment approach Buta main artery -- Thompson ** -- approach (1) It applied correspondingly and measured. 1mM The bottom of EGTA existence, 1microM cGMP was measured as a substrate. this invention compound dissolved by DMSO and, in addition to reaction mixture, saw inhibition activity. In addition, the last concentration of DMSO in reaction mixture was made into 4% or less.
[0202] (1) Thomson, W.J.and Strada, S.J., Cyclic Nucleotide Phosphodiesterase (PDE), Beating of the preparation Buta main artery of in Methods of Enzymatic analysis, vol 4, p127-234, and 1984 cGMP-PDE is carried out. Buffer A (mM Tris/HCl 20 --) 2mM Mg acetate and 1mM Dithiothreitol, 5mMEDTA, 1400TIU/Liter aprotinin, and 10 mg/l. leupeptin 1mM benzamidine, 0.2mMPMSF, and pH 7.5 ** is added 10 times. The homogenate was carried out. It is DEAE-Toyopearl 650S about the supernatant liquid obtained by carrying out centrifugal [of the

homogenate] in 100,000xg and 1 hour. It applied to the column (Tosoh, Tokyo, Japan). Buffer B (50 mM Tris/HCl, 0.1mMEGTA, 2mM Mg acetate, 1mM Dithiothreitol, 0.2mM PMSF, pH 7.5) 0.05 - 0.4M NaCl after washing a column It was eluted having applied gray JIENTO and CaM-independent cGMP-PDE fractionation was obtained.

[0203] 2. The experimental result in this invention compound is shown in the experimental result table 1.

[0204]

[Table 1]

[0205] this invention compound became clear [PDE and having cGMP-PDE inhibitory action especially] from the above-mentioned example of an experiment. That is, this invention compound became clear [having the effectiveness of raising the concentration of cGMP in the living body] by showing cGMP-PDE inhibitory action. Therefore, the nitrogen-containing heterocyclic compound which is this invention compound has cGMP-PDE inhibitory action effective in prevention and the therapy of an effective disease. If an example is given as these diseases, allergic diseases, such as ischemic heart disease, such as angina pectoris, myocardial infarction, chronic, and acute cardiac insufficiency, the pulmonary hypertension which may concur with the cor pulmonale, the other hypertension by all the origins, peripheral circulatory insufficiency, cerebral vascular insufficiency, cerebral function incompetence and bronchial asthma, atopic dermatitis, or allergic rhinitis, etc. can be mentioned, for example.

[0206] Moreover, what checks calmodulin-dependent PDE is contained in this invention compound group. The same possibility as a disease with effective above-mentioned cGMP-PDE inhibitory action of the disease with this effective operation is high, and it can be said also from this point that this invention compound is what can be used for prevention and the therapy of the above-mentioned disease.

[0207] Moreover, toxicity is low, and since this invention compound is expensive, this invention value is high [the compound / safety] also from this semantics.

[0208] When using this invention compound as such physic, a medicine is prescribed for the patient by internal use or parenteral administration. A dose changes with classes of an extent; patient's age of a symptom, sex, weight, the stage of susceptibility difference; medication method; administration, spacing, the property of physic pharmaceutical preparation, dispensing, and class; active principle etc., and is not limited especially.

[0209] the case of internal use -- usually -- an adult -- about 1-1,000mg per day, preferably, it is 10 - 100 mg still more preferably, and this is usually prescribed for the patient in 1 - 3 steps per about 5-500mg day. In injection, it is usually 1microg/kg - 3,000microg/kg, and it is about 3microg/kg - 1,000microg/kg preferably.

[0210] When preparing the solid preparations for taking orally, an excipient and after adding a binder, disintegrator, lubricant, a coloring agent, correctives, etc. if needed further, it considers as a tablet, a covering tablet, a granule, powder, a capsule, etc. with a conventional method at a chief remedy.

[0211] As an excipient, a lactose, corn starch, white soft sugar, grape sugar, sorbitol, crystalline cellulose, a silicon dioxide, etc., for example as a binder For example, polyvinyl alcohol, polyvinyl ether, ethyl cellulose, Methyl cellulose, gum arabic, tragacanth, gelatin, a shellac, Hydroxypropylcellulose, the hydroxypropyl methylcellulose, calcium citrate, a dextrin, pectin, etc. as lubricant For example, what is permitted that magnesium stearate, talc, a polyethylene glycol, a silica, hardening vegetable oil, etc. add in drugs as a coloring agent is used for the menthol, an aroma acid, mentha oil, borneol, a cinnamomi cortex pulveratus, etc. as correctives in the end of cocoa. Of course, these tablets and a granule are not hindered by coating suitably according to glycocalyx, gelatin clothes, and other need.

[0212] In preparing injections, pH regulator, a buffer, a suspending agent, a solubilizing agent, a stabilizing agent, an isotonizing agent, a preservative, etc. are added as occasion demands to a chief remedy, and it considers as a vein, hypodermically, and an intramuscular injection agent with a conventional method. It is also required in that case to consider as a freeze-drying object with a conventional method as occasion demands.

[0213] If the example as suspension is given, methyl cellulose, polysorbate 80, hydroxyethyl

cellulose, gum arabic, powdered tragacanth, carboxymethylcellulose sodium, polyoxyethylene sorbitan monolaurate, etc. can be mentioned, for example.
[0214] As a solubilizing agent, polyoxyethylene hydrogenated castor oil, polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, tuna gall, castor oil fatty-acid ethyl ester, etc. can be mentioned, for example.
[0215]
[Example] Next, although the example of this invention is hung up, it cannot be overemphasized that this invention does not have these things [being limited to seeing]. Moreover, in advance of an example, the example of manufacture of the raw material compound of the compound of this invention is hung up. In addition, in Me, an ethyl group and Bzl show benzyl and, as for a methyl group and Et, Ac shows an acetyl group.
[0216] Example of manufacture 12-ethoxycarbonyl-6-chloro quinazoline-4(3H)-ON [0217]
[Formula 79]
[0218] 2-amino-5-chloro benzamide 2.50g (0.0147 mols) is dissolved in pyridine 15ml, and they are the bottom of room temperature stirring, and ethyl oxalyl chloride. 2.0ml is dropped. The solvent was distilled off under reduced pressure after several hour stirring, and the residue obtained was used for the next reaction as it was.
[0219] Residue is dissolved in 50ml of acetic acids, 5ml of acetic anhydrides is added to this, and heating reflux is carried out one whole day and night. A solvent is distilled off under reduced pressure, ethanol is added to the crystal obtained, and a crystal is separated. It washed and was air-dry with ethanol and the ether, and 2.78g of light ****** of a title compound was obtained.
[0220] - ** Rate; 75% and ** Point; 239 - 240 **, Mass;253(M+H)+, and NMR delta (DMSO-d6); [1.36 (3H, t, J= 7.2Hz),] 4.39 (2H, q, J= 7.2Hz) 7.86 (1H, d, J= 8.8Hz), 7.92 (1H, dd, J= 8.8Hz, 2.4Hz), 8.11 (1H, d, J= 2.4Hz), 12.85 (1H, brs) example 14-chloro-6-cyano quinazoline [0221]
[Formula 80]
[0222] The heating reflux of 4-hydroxy-6-carbamoyl quinazoline 2g, 30ml of thionyl chlorides, and the mixture of 60ml of phosphorus oxychloride was carried out for 20 hours. It is ethyl acetate about the residue which condensed reaction mixture under reduced pressure and was obtained. It dissolved in 100ml. It is rinsing (150ml) about this. It condensed under reduced pressure after desiccation with magnesium sulfate the back, and the silica gel column chromatography was given. It is eluted with ethyl acetate and an acetone, and is 800mg about a title compound. It obtained.
[0223] - Molecular formula; C9H4N3Cl and (189.5) ** Rate; 40% and ** Point; >290 **, Mass;190 (M+1)+, and NMR delta (DMSO-d6); [7.79 (1H, d, J= 8.8Hz),] 8.16 (1H, dd, J= 8.8Hz, 2.0Hz), 8.26 (1H, s), 8.49 (1H, d, J= 2.0Hz) examples 22, 4-dichloro-6-cyano quinazoline [0224]
[Formula 81]
[0225] It is phosphorus oxychloride in 2 and 4-dihydroxy-6-carbamoyl quinazoline 12g and 48.8g of phosphorus pentachlorides. It suspended in 200ml and 70ml of thionyl chlorides, and heating reflux was carried out for 24 hours. It is ethyl acetate about the crystalline residue which condensed reaction mixture under reduced pressure and was obtained. 100ml and n-hexane It washes by 100ml and is a title compound. 6.8g was obtained.
[0226] - Molecular formula; C9H3Cl2N3 and ** Rate; 52% and ** Point; 161 - 163 **, Mass;224 (M+1)+, and NMR delta (CDCl3); [7.94 (1H, d, J= 8.0Hz),] 8.00 (1H, dd, J= 8.0Hz, 2.0Hz) 8.49 (example 32-ethoxycarbonyl -4, 6-dichloro quinazoline [0227]) (1H, d, J= 2.0Hz)
[Formula 82]
[0228] 2-ethoxycarbonyl-6-chloro quinazoline-4(3H)-ON 2.68g obtained in the example 1 of manufacture (0.0106 mols) 40ml of phosphorus oxychloride is made to suspend, and heating reflux is carried out for 1 hour. A solvent is distilled off under reduced pressure, residue is dissolved in ethyl acetate, and it washes with saturation sodium bicarbonate water. The organic layer was separated, with sulfuric anhydride magnesium, after desiccation, it filtered, bottom solvent distilling off of reduced pressure of the filtrate was carried out, and 2.82g of light ****** of a title compound was obtained.
[0229] - Yield (%);98 and melting point (degree-C);129 - 130, and Mass ; 271(M+1)+ and NMR delta (CDCl3); [1.50 (3H, t, J= 7.2Hz),] 4.60 (2H, q, J= 7.2Hz) 7.99 (1H, dd, J= 8.8Hz, 2.4Hz), 8.25

(1H, d, J= 8.8Hz), example of 8.34 (1H, d, J= 2.4Hz) reference 14-(3, 4-methylene dioxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0230]
[Formula 83]
[0231] 4-chloro - 6, 7, and 8-trimethoxy quinazoline 21.2g (0.083 mols), piperonyl amine 17.0g (0.112 mols), 13.5g (0.127 mols) of sodium carbonates Isopropyl alcohol It mixed to 400ml and heating reflux was carried out one whole day and night. Bottom solvent distilling off of reduced pressure of the reaction mixture was carried out, residue was recrystallized from ethyl acetate after purification with the silica gel column chromatography (ethyl acetate), and 21.3g of light yellow needle shape crystals of a title compound was obtained.
[0232] - Molecular formula; C19H19N3O5, yield (%);69 and melting point (degree-C);197 - 198, and Mass ; 370(M+H)+ and NMR delta (CDCl3) ; 3.94 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.76 (2H, d, J= 8.0Hz), 5.55 (1H, brs), 5.97 (2H, s), 6.64 (1H, s), The following compound was compounded according to the approach of 6.80 (1H, d, J= 8.0Hz), 6.87 (1H, d, J= 8.0Hz), 6.91 (1H, s), 8.66 (1H, s) examples 4 - the example 1 of 32 reference.
[0233] Example 44-benzylamino - 6, 7, 8-trimethoxy quinazoline [0234]
[Formula 84]
[0235] - Molecular formula; C18H19N3O3, yield (%);91 and melting point (degree-C);180 - 181, and Mass ; 326(M+H)+ and NMR delta (CDCl3);
3.94 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.87 (2H, d, J= 5.2Hz), 5.62 (1H, brs), 6.65 (1H, s), 7.4 (5H, m), 8.67 (1H, s) example 54-(4-methoxybenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0236]
[Formula 85]
[0237] - Molecular formula ; C19H21N3O4, yield (%);97 and melting point (degree-C);174 - 175, and Mass ; 356(M+H)+ and NMR delta (CDCl3); [3.82 (3H, s),] 3.93 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.79 (2H, d, J= 4.8Hz) 5.53 (1H, brs), 6.63 (1H, s), 6.92 (2H, d, J= 8.4Hz), 7.35 (2H, d, J= 8.4Hz), 8.67 (1H, s) example 64-(3-methoxybenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0238]
[Formula 86]
[0239] - Molecular formula ; C19H21N3O4, yield (%);89 and melting point (degree-C);142 - 143, and Mass ; 356(M+H)+ and NMR delta (CDCl3); [3.80 (3H, s),] 3.96 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.85 (2H, d, J= 4.8Hz) 5.96 (1H, brs), 6.76 (1H, s) 6.86 (1H, d, J= 8.0Hz), 6.99 (1H, d, J= 8.0Hz), 7.02 (1H, s), 7.29 (1H, t, J= 8.0Hz), 8.65 (1H, s) example 74-(4-nitrobenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0240]
[Formula 87]
[0241] - Molecular formula ; C18H18N4O5, yield (%);28 and melting point (degree-C);210 - 212, and Mass ; 371(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.05 (3H, s), 4.13 (3H, s), 5.01 (2H, d, J= 5.6Hz), 5.96 (1H, brs), 6.76 (1H, s), 7.54 (2H, d, J= 8.8Hz), 8.17 (2H, d, J= 8.8Hz), 8.62 (1H, s) example 84-(3-nitrobenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0242]
[Formula 88]
[0243] - Molecular formula ; C18H18N4O5, yield (%);30 and melting point (degree-C);159 - 160, and Mass ; 371(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.04 (3H, s), 4.12 (3H, s), 4.99 (2H, d, J= 5.6Hz), 6.06 (1H, brs), 6.79 (1H, s), 7.51 (1H, t, J= 8.0Hz), 7.76 (1H, d, J= 8.0Hz), 8.12 (1H, d, J= 8.0Hz), 8.22 (1H, s), 8.63 (1H, s) example 94-(4-chloro benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0244]
[Formula 89]
[0245] - Molecular formula ; C18H18N3O3Cl, yield (%);61 and melting point (degree-C);181 - 182, and Mass ; 360(M+H)+ and NMR delta (CDCl3); [3.94 (3H, s),] 4.03 (3H, s), 4.12 (3H, s), 4.85 (2H, d, J= 5.6Hz), 5.76 (1H, brs), 6.70 (1H, s), 7.32 (4H, brs), 8.64 (1H, s) example 104-(3-chloro benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0246]
[Formula 90]
[0247] - Molecular formula ; C18H18N3O3Cl, yield (%);85 and melting point (degree-C);161 - 162, and Mass ; 360(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.04 (3H, s), 4.13 (3H, s), 4.87 (2H, d, J= 5.2Hz), 5.66 (1H, brs), 6.68 (1H, s), 7.29 (3H, s), 7.39 (1H, s), 8.65 (1H, s) example 114-furfuryl amino - 6, 7, 8-trimethoxy quinazoline [0248]
[Formula 91]
[0249] - Molecular formula ; C16H17N3O4, yield (%);81 and melting point (degree-C);198 - 199,

and Mass ; 316(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.03 (3H, s), 4.12 (3H, s), 4.87 (2H, d, J= 5.2Hz), 5.67 (1H, brs), 6.37 (2H, m), 6.68 (1H, s), 7.42 (1H, s), 8.67 (1H, s) example 124-(4-picolyl) amino - 6, 7, 8-trimethoxy quinazoline [0250]
[Formula 92]
[0251] - Molecular formula ; C17H18N4O3, yield (%);76 and melting point (degree-C);166 - 168, and Mass ; 327(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.05 (3H, s), 4.12 (3H, s), 4.92 (2H, d, J= 6.0Hz), 6.06 (1H, brs), 6.80 (1H, s), 7.28 (2H, d, J= 6.0Hz), 8.55 (2H, d, J= 6.0Hz), 8.62 (1H, s) example 134-(4-ethyl benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0252]
[Formula 93]
[0253] - Molecular formula ; C20H23N3O3, yield (%);88 and melting point (degree-C);195 - 196, and Mass ; 354(M+H)+ and NMR delta (CDCl3); [1.25 (3H, t, J= 7.6Hz),] 2.67 (2H, q, J= 7.6Hz) 3.94 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.83 (2H, d, J= 4.8Hz), 5.56 (1H, brs), 6.63 (1H, s), 7.23 (2H, d, J= 8.0Hz), 7.35 (2H, d, J= 8.0Hz), 8.67 (1H, s) example 144-(indan-5-ylmethyl) amino - 6, 7, 8-trimethoxy quinazoline [0254]
[Formula 94]
[0255] - Molecular formula ; C21H23N3O3, yield (%);61 and melting point (degree-C);198 - 199, and Mass ; 366(M+H)+ and NMR delta (CDCl3); [2.11 (2H, quintet, J= 7.2Hz),] 2.93 (4H, t, J= 7.2Hz) 3.94 (3H, s), 4.04 (3H, s), 4.14 (3H, s), 4.83 (2H, d, J= 4.4Hz), 5.55 (1H, brs), 6.64 (1H, s), 7.2-7.3 (3H, m), 8.68 (1H, s) example 154-(4-carboxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0256]
[Formula 95]
[0257] - Molecular formula ; C19H19N3O5, yield (%);86, and melting point (degree-C);227 -228 (decomposition)
- Mass ; 370(M+H)+ and NMR delta (DMSO-d6); [3.89 (3H, s),] 3.92 (3H, s), 3.98 (3H, s), 4.86 (2H, d, J= 5.6Hz), 7.46 (2H, d, J= 8.0Hz) 7.54 (1H, s), 7.90 (2H, d, J= 8.0Hz), 8.35 (1H, s), 8.67 (1H, brs) example 164-(3-hydroxy methylbenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0258]
[Formula 96]
[0259] - Molecular formula ; C19H21N3O4, yield (%);86, and melting point (degree-C); amorphous and Mass ; 356(M+H)+ and NMR delta (CDCl3); [3.93 (3H, s),] 4.03 (3H, s), 4.12 (3H, s), 4.70 (2H, s), 4.86 (2H, d, J= 5.2Hz), 5.82 (1H, brs), 6.72 (1H, s), 7.3-7.4 (4H, m), 8.63 (1H, s) example 174-(3, 4-dichloro benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0260]
[Formula 97]
[0261] - Molecular formula ; C18H17N3O3Cl2, yield (%);85 and melting point (degree-C);205 - 206, and Mass ; 394(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.04 (3H, s), 4.12 (3H, s), 4.84 (2H, d, J= 5.6Hz), 5.88 (1H, brs), 6.74 (1H, s), 7.24 (1H, d, J= 8.4Hz), 7.40 (1H, d, J= 8.4Hz), 7.47 (1H, s), 8.63 (1H, s) example 184-(3, 4-difluorobenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0262]
[Formula 98]
[0263] - Molecular formula ; C18H17N3O3F2, yield (%);96 and melting point (degree-C);175 - 177, and Mass ; 362(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.04 (3H, s), 4.13 (3H, s), 4.85 (2H, d, J= 5.2Hz), 5.73 (1H, brs), 6.69 (1H, s), 7.1-7.3 (3H, m), 8.64 (1H, s) example 194-(3, 4-dimethoxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0264]
[Formula 99]
[0265] - Molecular formula ; C20H23N3O5, yield (%);32 and melting point (degree-C);171 - 172, and Mass ; 386(M+H)+ and NMR delta (CDCl3); [3.87 (3H, s),] 3.89 (3H, s) 3.94 (3H, s) 4.03 (3H, s), 4.13 (3H, s) 4.79 (2H, d, J= 5.2Hz), 5.67 (1H, brs) 6.69 (1H, s) 6.86 (1H, d, J= 8.8Hz) 6.96 (1H, s) 6.98 (1H, d, J= 8.8Hz) 8.67 (1H, s)
Example 204-(4-hydroxy-3-methoxybenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0266]
[Formula 100]
[0267] - Molecular formula ; C19H21N3O5, yield (%);16, and melting point (degree-C);201 -202 (decomposition)
- Mass ; 372(M+H)+ and NMR delta (CDCl3); [3.88 (3H, s),] 3.96 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.78 (2H, d, J= 5.2Hz) 6.00 (1H, brs), 6.77 (1H, s), 6.91 (1H, s), 6.92 (1H, s), 6.97 (1H, s), 8.65 (1H, s) example 214-(3-allyl compound-4-methoxy methoxybenzyl) amino - 6, 7, 8-trimethoxy

quinazoline [0268]
[Formula 101]
[0269] - Molecular formula ; C23H27N3O5, yield (%);49 and melting point (degree-C);120 - 121, and Mass ; 426(M+H)+ and NMR delta (CDCl3); [3.41 (2H, d, J= 6.8Hz),] 3.48 (3H, s), 3.94 (3H, s), 4.03 (3H, s), 4.12 (3H, s) 4.77 (2H, d, J= 5.2Hz), 5.06 (2H, m), 5.21 (2H, s), 5.78 (1H, brs), 5.98 (1H, m), 6.71 (1H, s), 7.07 (1H, d, J= 8.4Hz), 7.23 (1H, s), 7.24 (1H, d, J= 8.4Hz), 8.65 (1H, s) example 224-(4-benzyloxy-3-nitrobenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0270]
[Formula 102]
[0271] - Molecular formula ; C25H24N4O6, yield (%);81 and melting point (degree-C);181 - 182, and Mass ; 477(M+1)+ and NMR delta (CDCl3); [3.98 (3H, s),] 4.03 (3H, s), 4.10 (3H, s), 4.85 (2H, d, J= 5.2Hz), 5.21 (2H, s), 6.54 (1H, brs), 6.93 (1H, s), 7.06 (1H, d, J= 8.4Hz), 7.30-7.45 (5H, m), 7.60 (1H, dd, J= 8.4Hz, 2.4Hz), 7.87 (1H, d, J= 2.4Hz), 8.61 (1H, s) example 234-(4-chloro-3-nitrobenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0272]
[Formula 103]
[0273] - Molecular formula ; C18H17N4O5Cl, yield (%);88, and melting point (degree-C);218 -219 (decomposition)
- Mass ; 405(M+H)+ and NMR delta (CDCl3); [3.98 (3H, s),] 4.04 (3H, s), 4.13 (3H, s), 4.93 (2H, d, J= 6.0Hz), 5.98 (1H, brs), 6.75 (1H, s), 7.50 (1H, d, J= 8.4Hz), 7.58 (1H, dd, J= 8.4Hz, 2.0Hz), 7.87 (1H, d, J= 2.0Hz), 8.61 (1H, s) example 244-(2-propoxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0274]
[Formula 104]
[0275] - Molecular formula ; C21H25N3O4, yield (%);80 and melting point (degree-C);139 - 140, and Mass ; 384(M+H)+ and NMR delta (CDCl3); [1.07 (3H, t, J= 7.4Hz),] 1.85 (2H, m), 3.95 (3H, s), 4.02 (3H, s), 4.02 (2H, t, J= 6.4Hz) 4.10 (3H, s), 4.89 (2H, d, J= 5.6Hz) 6.72 (1H, s), 6.9 (2H, m), 7.28 (1H, m), 7.38 (1H, d, J= 7.2Hz), 8.64 (1H, s) example 254-(2, 4, 6-trimethoxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0276]
[Formula 105]
[0277] - Molecular formula ; C21H25N3O6, yield (%);64 and melting point (degree-C);213 - 215, and Mass ; 416(M+H)+ and NMR delta (CDCl3); [3.85 (9H, s),] 3.92 (3H, s), 4.01 (3H, s), 4.11 (3H, s), 4.79 (2H, d, J= 4.4Hz), 5.65 (1H, brs), 6.20 (2H, s), 6.60 (1H, s), 8.68 (1H, s) example 264-(3, 4, 5-trimethoxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0278]
[Formula 106]
[0279] - Molecular formula ; C21H25N3O6, yield (%);60 and melting point (degree-C);153 - 154, and Mass ; 416(M+H)+ and NMR delta (CDCl3); [3.85 (9H, s),] 3.97 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.80 (2H, d, J= 5.6Hz), 6.66 (2H, s), 6.80 (1H, s), 8.66 (1H, s) example 274-[2-(4-nitrophenyl) ethyl] amino - 6, 7, 8-trimethoxy quinazoline [0280]
[Formula 107]
[0281] - Molecular formula ; C19H20N4O5, yield (%);58 and melting point (degree-C);152 - 153, and Mass ; 385(M+H)+ and NMR delta (CDCl3); [3.18 (2H, t, J= 7.2Hz),] 3.92 (3H, s), 3.96 (3H, m), 4.04 (3H, s), 4.13 (3H, s), 5.57 (1H, brs), 6.58 (1H, s), 7.41 (2H, d, J= 8.8Hz), 8.17 (2H, d, J= 8.8Hz), 8.66 (1H, s) example 284-[2-(imidazole-4-IRU) ethyl] amino - 6, 7, 8-trimethoxy quinazoline [0282]
[Formula 108]
[0283] - Molecular formula ; C16H19N5O3, yield (%);77, and melting point (degree-C);164 -166 (decomposition)
- Mass ; 330(M+H)+ and NMR delta (DMSO-d6); [3.00 (2H, t, J= 7.2Hz),] 3.81 (2H, m), 3.87 (3H, s), 3.92 (3H, s), 3.97 (3H, s), 7.25 (1H, s), 7.56 (1H, s), 8.39 (1H, s), 8.45 (1H, s), and 8.50 (1H, brs) example 294-(6, 7-dimethoxy - 1, 2, 3, 4-tetrahydroisoquinoline-2-IRU)- 6, 7, and 8-trimethoxy quinazoline [0284]
[Formula 109]
[0285] - Molecular formula ; C22H25N3O5, yield (%);79 and melting point (degree-C);157 - 158, and Mass ; 412(M+H)+ and NMR delta (CDCl3); [3.11 (2H, t, J= 5.8Hz),] 3.87 (3H, s), 3.89 (3H, s), 3.96 (2H, t, J= 5.8Hz), 3.99 (3H, s), 4.07 (3H, s), 4.14 (3H, s), 4.80 (2H, s), 6.67 (1H, s), 6.71 (1H, s), 7.03 (1H, s), 8.74 (1H, s) example 304-[4-(1-hydroxyethyl) benzyl] amino-6-methoxy quinazoline

[0286]
[Formula 110]
[0287] - Molecular formula ; C18H19N3O2, yield (%);46, and melting point (degree-C); amorphous and Mass ; 310(M+H)+ and NMR delta (CDCl3); [1.47 (2H, d, J= 6.4Hz),] 3.91 (3H, s) 4.87 (2H, d, J= 5.2Hz), 4.84-4.94 (1H, m), 7.34-7.42 (6H, m), 7.59 (1H, brs), 7.79 (1H, d, J= 8.8Hz), 8.52 (1H, s) example 314-[2-(3, 4-methylenedioxyphenyl) pyrrolidino]-6-methoxy quinazoline [0288]
[Formula 111]
[0289] - Molecular formula ; C20H19N3O3, yield (%);85, and melting point (degree-C); oil and Mass ; 350(M+1)+ and NMR delta (CDCl3); [1.95-2.10 (3H, m),] 2.37 (1H, m), 3.58 (3H, s), 4.05-4.20 (2H, m), 5.58 (1H, m), 5.93 (1H, s), 5.94 (1H, s), 6.78 (1H, d, J= 8.4Hz) 6.84 (1H, s), 6.85 (1H, d, J= 8.4Hz) 7.30 (1H, d, J= 10.0Hz), 7.35 (1H, s), 7.74 (1H, d, J= 10.0Hz), 8.53 (1H, s) example 324-(4-methoxy-3-nitrobenzyl) amino-6-methoxy quinazoline [0290]
[Formula 112]
[0291] - Molecular formula ; C17H16N4O4, yield (%);22, and melting point (degree-C);205 -206 (decomposition)
- Mass ; 341(M+1)+ and NMR delta (CDCl3); [3.93 (3H, s),] 3.94 (3H, s) 4.91 (2H, d, J= 6.0Hz), 7.07 (1H, dd, J= 8.4Hz, 1.2Hz) 7.21 (1H, d, J= 1.2Hz), 7.39 (1H, dd, J= 9.2Hz, 2.4Hz) 7.53 (1H, d, J= 2.4Hz), 7.75 (1H, d, J= 9.2Hz), 7.82 (1H, d, J= 8.4Hz), 8.03 (1H, brs), example of 8.51 (1H, s) reference 24-(3, 4-methylene dioxy benzyl) amino-6-methylthio quinazoline [0292]
[Formula 113]
[0293] 4-chloro-6-methylthio quinazoline 4.12g (0.0196 mols), piperonyl amine 3.70g (0.0245 mols), 3.50g (0.0330 mols) of sodium carbonates Isopropyl alcohol It mixes to 100ml and heating reflux is carried out one whole day and night. Bottom solvent distilling off of reduced pressure of the reaction mixture was carried out, residue was recrystallized from the chloroform-n-hexane after purification with the silica gel column chromatography (ethyl-acetate-n-hexane), and 5.32g of light ****** of a title compound was obtained.
[0294] - Molecular formula ; C17H15O2N3S, yield (%);83 and melting point (degree-C);174 - 175, and Mass ; 326(M+H)+ and NMR delta (CDCl3); [2.59 (3H, s),] 4.79 (2H, d, J= 5.6Hz) 5.93 (2H, s), 6.77 (1H, d, J= 8.0Hz) 6.89 (1H, d, J= 8.0Hz), 6.94 (1H, s) 7.62 (1H, dd, J= 8.8Hz, 2.0Hz), The following compound was compounded according to the approach of 7.75 (1H, d, J= 8.8Hz), 7.97 (1H, d, J= 2.0Hz), 8.10 (1H, brs), and the example 2 of 8.56 (1H, s) example 33 reference.
[0295] 4-(3, 4-dichloro benzyl) amino-6-methylthio quinazoline [0296]
[Formula 114]
[0297] - Molecular formula ; C16H13N3SCl2, yield (%);85 and melting point (degree-C);184 - 185, and Mass ; 350(M+H)+ and NMR delta (CDCl3); [2.61 (3H, s),] 4.83 (2H, d, J= 5.6Hz) 7.28 (1H, dd, J= 8.4Hz, 2.0Hz), 7.40 (1H, d, J= 8.4Hz) 7.51 (1H, d, J= 2.0Hz), 7.64 (1H, dd, J= 8.8Hz, 2.0Hz) 7.76 (1H, d, J= 8.8Hz), 7.97 (1H, d, J= 2.0Hz), 8.19 (1H, brs), 8.55 (1H, s) example 344-(4-chloro-3-nitrobenzyl) amino-6-chloro quinazoline [0298]
[Formula 115]
[0299] 4 and 6-dichloro quinazoline 3.00g (0.015 mols), 4-chloro-3-nitrobenzyl amine 3.80g (0.0170 mols) of hydrochlorides Isopropyl alcohol It is made to dissolve in 100ml and triethylamine 15ml, and heating reflux is carried out one whole day and night. Bottom solvent distilling off of reduced pressure was carried out, residue was recrystallized from the chloroform-n-hexane after purification with the silica gel column chromatography (chloroform-ethyl acetate), and 4.85g of light ****** of a title compound was obtained.
[0300] - Molecular formula ; C15H10N4O2Cl2, yield (%);92 and melting point (degree-C);199 - 200, and Mass ; 349(M+H)+ and NMR delta (CDCl3); [4.85 (2H, d, J= 6.0Hz),] 7.49 (1H, d, J= 8.4Hz) 7.61 (1H, dd, J= 8.4Hz, 2.0Hz), 7.66 (1H, dd, J= 8.8Hz, 2.0Hz) 7.76 (1H, d, J= 8.8Hz), The following compound was compounded according to the approach of 7.96 (1H, d, J= 2.0Hz), 8.20 (1H, d, J= 2.0Hz), 8.23 (1H, brt, J= 6.0Hz), and 35 to 8.58 (1H, s) example 37 example 34.
[0301] Example 354-(3, 4-dichloro benzyl) amino-6-chloro quinazoline [0302]
[Formula 116]
[0303] - Molecular formula ; C15H10N3Cl3, yield (%);72 and melting point (degree-C);215 - 216, and Mass ; 338(M+H)+ and NMR delta (CDCl3); [4.85 (2H, d, J= 5.6Hz),] 5.94 (1H, brs) 7.24 (1H,

d, J= 8.4Hz), 7.43 (1H, d, J= 8.4Hz) 7.70 (1H, d, J= 9.2Hz), 7.72 (1H, s), 7.83 (1H, d, J= 9.2Hz), 8.68 (1H, s) example 364-(3, 4-dimethoxy benzyl) amino-6-chloro quinazoline [0304]
[Formula 117]
[0305] - molecular formula ; C17H16N3O2Cl, yield (%);73, and melting point (degree-C);174 - 175 and Mass ; 330(M+H)+ and NMR delta (CDCl3);3.87 (6H, s) -- 4.78 (2H, d, J= 5.2Hz) 6.85 (1H, d, J= 8.0Hz), 6.96 (1H, d, J= 8.0Hz) 6.98 (1H, s), 7.34 (1H, brs) 7.65 (1H, dd, J= 9.2Hz, 2.0Hz), 7.78 (1H, d, J= 9.2Hz), 8.08 (1H, d, J= 2.0Hz), 8.65 (1H, s) example 374-(2-methoxy -2, 3-dihydrobenzofuran-5-IRU) methylamino-6-chloro quinazoline [0306]
[Formula 118]
[0307] - Molecular formula ; C18H16N3O2Cl, yield (%);53 and melting point (degree-C);178 - 179, and Mass ; 342 (MH+) and NMR delta (DMSO-d6); [2.88 (1H, dd, J= 2.0Hz, 17.0Hz),] 3.28-3.34 (1H, m), 4.68 (1H, d, J= 5.7Hz), 5.68 (1H, dd, J= 2.0Hz, 6.6Hz) 6.79 (1H, d, J= 8.2Hz), 7.14 (1H, d, J= 8.2Hz) 7.24 (1H, s), 7.70 (1H, d, J= 9.0Hz) 7.79 (1H, dd, J= 2.2Hz, 9.0Hz), 8.46 (1H, d, J= 2.2Hz), 8.48 (1H, s), example of 8.82 (1H, t, J= 5.7Hz) reference 34-(3, 4-methylene dioxy benzyl) amino-6-cyano quinazoline [0308]
[Formula 119]
[0309] 4-chloro-6-cyano quinazoline 140mg Isopropyl alcohol 15ml, triethylamine 75mg, and piperonyl amine 125mg In addition, heating reflux was carried out for 5 hours. Precipitate was separated and the silica gel column chromatography was given. It is eluted with ethyl acetate and is 200mg about a title compound. It obtained.
[0310] - Molecular formula ; C17H12N4O2, yield (%);89 and melting point (degree-C);243 - 244, and Mass ; 305+ (M+1) and NMR delta (DMSO-d6); [4.67 (2H, d, J= 5.6Hz),] 5.96 (2H, s), 6.84 (2H, s), 6.95 (1H, s), The following compounds were compounded according to the approach of 7.77 (1H, d, J= 8.4Hz), 8.56 (1H, s), 8.89 (1H, s), 9.04 (1H, br) examples 38 - the example 3 of 42 reference.
[0311] Example 384-[3-(1-imidazolyl) propyl] amino-6-cyano quinazoline [0312]
[Formula 120]
[0313] - Molecular formula ; C15H14N6, yield (%);22 and melting point (degree-C);196 - 197, and Mass m/e ; 279 (M+1) and NMR delta (CDCl3); [2.27 (2H, quintet, J= 6.4Hz),] 3.66 (2H, q, J= 6.4Hz) 4.17 (2H, t, J= 6.4Hz), 7.07 (1H, s), 7.11 (1H, s), 7.82 (1H, s), 7.82 (1H, s), 8.09 (1H, s), 8.37 (1H, brs), 8.66 (1H, s), 8.84 (1H, s) and a molecular formula ; C20H15N3O2, yield (%);45, and melting point (degree-C);265 (decomposition)
- Mass ; 330(M+1)+ and NMR delta (DMSO-d6); [4.92 (2H, d, J= 6.0Hz),] 5.97 (2H, s) 6.88 (1H, d, J= 8.0Hz), 6.94 (1H, dd, J= 8.0Hz, 1.6Hz) 7.06 (1H, d, J= 1.6Hz), 7.68- 7.81 (2H, m) and 8.11 (1H, d, J= 8.4Hz) -- 8.21 (1H, d, J= 8.4Hz), 8.33 (1H, s), 8.90 (1H, s), 9.36 (1H, s), the 11.09 (1H, br) example 394-(3, 4, 5-trimethoxy benzyl) amino -6, 7-methylene dioxy quinazoline [0314]
[Formula 121]
[0315] - Molecular formula ; C19H19N3O5, yield (%);59 and melting point (degree-C);240 - 241, and Mass ; 370(M+1)+ and NMR delta (DMSO-d6); [3.61 (3H, s),] 3.70 (6H, s) 4.65 (2H, d, J= 6.0Hz), 6.16 (2H, s), 6.675 (2H, s), 7.06 (1H, s), 7.72 (1H, s), 8.23 (1H, brt, J= 6.0Hz), and 8.30 (1H, s) example 404-(3, 4-methylene dioxy benzamide)- 6, 7, and 8-trimethoxy quinazoline [0316]
[Formula 122]
[0317] - Molecular formula ; C19H17N3O6, yield (%);13 and melting point (degree-C);190 - 192, and Mass ; 384(M+H)+ and NMR delta (CDCl3); [4.10 (6H, s),] 4.12 (3H, s), 6.07 (2H, s), 6.91 (1H, d, J= 8.0Hz), 7.86 (1H, s), 7.90 (1H, s), 8.06 (1H, d, J= 8.0Hz), 8.18 (1H, s) example 414-(3, 4-methylene dioxy benzyl) oxy-- 6, 7, 8-trimethoxy quinazoline [0318]
[Formula 123]
[0319] - Molecular formula ; C19H18N2O6, yield (%);49 and melting point (degree-C);141 - 142, and Mass ; 371(M+H)+ and NMR delta (CDCl3); [3.97 (3H, s),] 4.05 (3H, s) 4.13 (3H, s) 5.53 (2H, s), 5.99 (2H, s) 6.84 (1H, d, J= 8.0Hz) 7.00 (1H, dd, J= 8.0Hz, 2.0Hz) 7.02 (1H, d, J= 2.0Hz) 7.20 (1H, s) 8.74 (1H, s)
Example 424-(3, 4-methylene dioxy benzyl) oxy--6-methylthio quinazoline [0320]
[Formula 124]
[0321] - Molecular formula ; C17H14N2O3Cl, yield (%);69 and melting point (degree-C);104 - 105,

and Mass ; 327(M+H)+ and NMR delta (CDCl3); [2.59 (3H, s),] 5.56 (2H, s), 6.00 (2H, s), 6.85 (1H, d, J= 8.0Hz), 7.01 (1H, dd, J= 8.0Hz, 1.6Hz) 7.03 (1H, d, J= 1.6Hz), 7.72 (1H, dd, J= 8.8Hz, 1.6Hz), 7.88 (1H, d, J= 8.8Hz), 7.89 (1H, d, J= 1.6Hz), 8.78 (1H, s) examples 432 and 4, 6-trimethoxy quinazoline [0322]
[Formula 125]
[0323] 2, 4-dichloro-6-methoxy quinazoline Methanol 150 ml is made to suspend 5.0g (0.022 mols), and it is sodium hydride. Heating reflux is carried out after adding 3.5g gradually. Vacuum concentration of the reaction mixture is carried out several hours after, water is added and precipitated crystal is separated, and it washes with water, it is air-dry, and is rough ****** of a title compound. 4.8g was obtained.
[0324] - Melting point (degree-C);143 - 144, and Mass ; 221(M+1)+ and NMR delta (CDCl3); [3.90 (3H, s),] 4.08 (3H, s), 4.18 (3H, s), 7.36 (1H, d, J= 2.8Hz), 7.39 (1H, dd, J= 8.8Hz, 2.8Hz), 7.67 (1H, d, J= 2.8Hz) examples 442, 4-screw benzyloxy-6-methoxy quinazoline [0325]
[Formula 126]
[0326] Benzyl alcohol 3ml is dissolved in tetrahydrofuran 50ml, and it is sodium hydride. 2 and 4-dichloro-6-methoxy quinazoline 2.50g after adding 1.0g and stirring at 40-50 degrees C for 30 minutes (0.0109 mols) In addition, heating reflux is carried out for several hours. Water is added to reaction mixture, chloroform extracts, and an organic layer is dried with sulfuric anhydride magnesium. The bottom solvent of filtration and reduced pressure was distilled off, the crystal obtained was recrystallized from the chloroform-n-hexane, and 3.84g of ****** of a title compound was obtained.
[0327] - yield (%);95 and melting point (degree-C);144 - 145 and Mass ; 373(M+1)+ and NMR delta (CDCl3);3.87 (3H, s) -- The following compound was compounded according to the approach of 5.53 (2H, s), 5.62 (2H, s), 7.31-7.55 (12H, m), and 7.70 (1H, d, J= 8.8Hz) example 45 examples 43-44.
[0328] 2, 6-dichloro-4-benzylamino quinazoline [0329]
[Formula 127]
[0330] - Molecular formula ; C15H11N3Cl2, yield (%);77 and melting point (degree-C);227 - 228, and NMR delta (CDCl3); [4.85 (2H, d, J= 5.2Hz),] 5.97 (1H, brs) 7.33-7.43 (5H, m), 7.62 (1H, d, J= 2.0Hz) 7.68 (1H, dd, J= 8.8Hz, 2.0Hz), 7.74 (1H, d, J= 8.8Hz) 2.75 (3H, s), 4.80 (2H, d, J= 5.2Hz), 5.96 (2H, s) 6.80 (1H, d, J= 8.0Hz), 6.89 (1H, d, J= 8.0Hz), 6.91 (1H, s), 7.06 (1H, brs), 7.64 (1H, d, J= 8.8Hz), 7.98 (1H, d, J= 8.8Hz) 8.43 (1H, s) 8.74 (1H, s)
Example of reference 42-formyl-4-(3, 4-methylene dioxy benzyl) amino-6-methoxy quinazoline [0331]
[Formula 128]
[0332] Oxalyl chloride To 1.0ml (11 millimol) 10ml solution of methylene chlorides, it is bottom dimethyl sulfoxide of -78-degree-C stirring. 1.5ml 5ml solution of methylene chlorides is dropped. - It is after stirring and 2 for 15 minutes at 78 degrees C. - A hydroxymethyl-4-(3, 4-methylene dioxy benzyl) amino-6-methoxy quinazoline 0.74g (2.2 millimol) dimethyl sulfoxide 7ml solution is dropped. - Stir for 30 minutes, triethylamine 5ml being dropped after stirring for 20 minutes at 78 degrees C, and carrying out a temperature up to a room temperature. Water was added to reaction mixture, chloroform extracted, the organic layer was filtered after desiccation with sulfuric anhydride magnesium, bottom solvent distilling off of reduced pressure of the filtrate was carried out, and 0.74g of rough blackish brown oily matter of a title compound was obtained.
[0333] - Molecular formula ; C18H15N3O4 and yield (%); quantitive and NMR delta (CDCl3); [3.93 (3H, s),] 4.86 (2H, d, J= 5.6Hz) 5.95 (2H, s), 6.28 (1H, brs) 6.78 (1H, d, J= 8.0Hz), 6.89 (1H, dd, J= 8.0Hz, 1.6Hz) 6.92 (1H, d, J= 1.6Hz), The following compounds were obtained according to the approach of 7.09 (1H, d, J= 2.8Hz), 7.47 (1H, dd, J= 9.2Hz, 2.8Hz), 7.97 (1H, d, J= 9.2Hz), 10.02 (1H, s) examples 46 - the example 4 of 48 reference.
[0334] Example 464-(3-formyl benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0335]
[Formula 129]
[0336] - Molecular formula ; C19H19N3O4 and yield (%); quantitive, melting point (degree-C); oil, and NMR delta (CDCl3); [3.96 (3H, s),] 4.04 (3H, s), 4.13 (3H, s), 4.97 (2H, d, J= 5.6Hz), 5.97 (1H, brt, J= 5.6Hz) 6.76 (1H, s), 7.53 (1H, t, J= 7.6Hz) 7.70 (1H, d, J= 7.6Hz), 7.81 (1H, d, J= 7.6Hz),

7.91 (1H, s), 8.64 (1H, s), 10.00 (1H, s) example 474-(3-carboxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0337]
[Formula 130]
[0338] - Molecular formula ; C19H19N3O5, yield (%);45, and melting point (degree-C);245 -246 (decomposition)
- Mass ; 370(M+H)+ and NMR delta (DMSO-d6); [3.89 (3H, s),] 3.93 (3H, s), 3.98 (3H, s), 4.86 (2H, d, J= 5.6Hz), 7.46 (1H, d, J= 7.6Hz) 7.56 (1H, s), 7.62 (1H, d, J= 7.6Hz), 7.83 (1H, d, J= 7.6Hz), 7.95 (1H, s), 8.39 (1H, s), 8.83 (1H, brs) example 484-(4-acetyl benzyl) amino-6-methoxy quinazoline [0339]
[Formula 131]
[0340] - molecular formula ; C18H17N3O2, yield (%);41, and melting point (degree-C);204 - 206 and Mass ; 308(M+H)+ and NMR delta (CDCl3);2.60 (3H, s) -- 3.91 (3H, s) 4.97 (2H, d, J= 5.6Hz), 5.96 (1H, brs), 6.98 (1H, s), 7.42 (1H, d, J= 9.2Hz), 7.50 (2H, d, J= 8.0Hz) 7.82 (1H, d, J= 9.2Hz), 7.94 (2H, d, J= 8.0Hz), example 52 of 8.61 (1H, s) reference - Hydroxy imino methyl-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinazoline [0341]
[Formula 132]
[0342] 2 - To a formyl-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinazoline 1.00g (2.93 millimol) ethanol 30ml solution, they are 0.60g of hydroxylamine hydrochlorides, and 1-N sodium-hydroxide water solution. 3.0ml is added and it stirs for 30 minutes at 60 degrees C. Precipitated crystal was separated after radiationnal cooling, it washed and was air-dry by ethanol and n-hexane, and 1.00g of white ** of a title compound was obtained.
[0343] - Molecular formula ; C17H13N4O3Cl, yield (%);96, and melting point (degree-C);245 -246 (decomposition)
- Mass ; 357 (M+1) and NMR delta (DMSO-d6); [4.69 (2H, d, J= 6.0Hz),] 5.96 (2H, s) 6.84 (1H, d, J= 7.6Hz), 6.91 (1H, d, J= 7.6Hz, 1.6Hz) 7.05 (1H, d, J= 1.6Hz), 7.72 (1H, d, J= 8.8Hz) 7.78 (1H, dd, J= 8.8Hz, 2.0Hz), The following compounds were obtained according to the approach of 7.96 (1H, s), 8.45 (1H, d, J= 2.0Hz), 8.91 (1H, brt, J= 6.0Hz), 11.83 (1H, s) examples 49 - the example 5 of 50 reference.
[0344] Example 494-(3-hydroxy imino methylbenzyl) amino - 6, 7, 8-trimethoxy quinazoline
[0345]
[Formula 133]
[0346] - Molecular formula ; C19H20N4O4, yield (%);56, and melting point (degree-C);231 -232 (decomposition)
- Mass ; 369(M+H)+ and NMR delta (DMSO-d6); [3.88 (3H, s),] 3.91 (3H, s), 3.98 (3H, s), 4.80 (2H, d, J= 6.0Hz), 7.3-7.5 (3H, m), 7.52 (1H, s), 7.60 (1H, s), 8.11 (1H, s), 8.35 (1H, s), 8.60 (1H, brs), 11.17 (1H, s) example 504-[4-(1-hydroxy imino ethyl) benzyl] amino-6-methoxy quinazoline
[0347]
[Formula 134]
[0348] - molecular formula ; C18H18N4O2 and yield (%); -- quantitive - melting point (degree-C);245 -246 (decomposition)
- Mass ; 323(M+H)+ and NMR delta (DMSO-d6); [2.13 (3H, s),] 3.95 (3H, s) 4.97 (2H, d, J= 5.6Hz), 7.44 (2H, d, J= 8.4Hz) 7.63 (2H, d, J= 8.4Hz), 7.68 (1H, dd, J= 9.2Hz, 2.8Hz) 7.83 (1H, d, J= 9.2Hz), 8.14 (1H, d, J= 2.8Hz), 8.84 (1H, s), 10.75 (1H, brs), 11.18 (1H, s) example 514-(3-amino-4-chloro benzyl) amino-6-chloro quinazoline [0349]
[Formula 135]
[0350] The heating reflux of 4-(4-chloro-3-nitrobenzyl) amino-6-chloro quinazoline 1.00g (2.86 millimol), 0.85g of iron powder, 10ml of acetic acids, and the ethanol 50ml mixture is carried out for several hours. Bottom solvent distilling off of reduced pressure was carried out, the silica gel column chromatography (ethyl-acetate-n-hexane) refined residue, and 0.91g of light ****** of a title compound was obtained.
[0351] - molecular formula ; C15H12N4Cl2 and yield (%); -- quantitive - melting point (degree-C);226 -229 (decomposition)
- Mass ; 319(M+H)+ and NMR delta (CDCl3); [4.19 (2H, brs),] 4.73 (2H, d, J= 6.0Hz) 6.71 (1H, dd, J= 8.0Hz, 2.0Hz), 6.83 (1H, d, J= 2.0Hz) 7.18 (1H, d, J= 8.0Hz), 7.64 (1H, dd, J= 8.8Hz, 2.0Hz) 7.72

(1H, brs), 7.74 (1H, d, J= 8.8Hz), 8.19 (1H, d, J= 2.0Hz), 8.60 (1H, s) example 524-(4-chloro-3-formamide benzyl) amino-6-chloro quinazoline [0352]
[Formula 136]
[0353] 4-(3-amino-4-chloro benzyl) amino-6-chloro quinazoline 0.90g (2.82 millimol) obtained in the example 51 was dissolved in 15ml of formic acid, 1ml of acetic anhydrides was added and room temperature stirring was carried out for several hours. Bottom solvent distilling off of reduced pressure was carried out, residue was recrystallized from ethyl acetate after purification with the silica gel column chromatography (ethyl acetate), and 0.64g of light ****** of a title compound was obtained.
[0354] - Molecular formula ; C16H12N4OCl2, yield (%);65 and melting point (degree-C);229 - 230, and Mass ; 347(M+H)+ and NMR delta (DMSO-d6); [4.74 (2H, d, J= 5.6Hz),] 7.15 (1H, dd, J= 8.4Hz, 2.0Hz) 7.43 (1H, d, J= 8.4Hz), 7.72 (1H, d, J= 8.8Hz) 7.80 (1H, dd, J= 8.8Hz, 2.0Hz), 8.16 (1H, d, J= 2.0Hz) 8.32 (1H, d, J= 2.0Hz), 8.45 (1H, s), 8.46 (1H, s), 8.95 (1H, brs), 9.83 (1H, brs) example 534-(3-formamide-4-methoxybenzyl) amino-6-chloro quinazoline [0355]
[Formula 137]
[0356] Carrying out the heating reflux of 4-(3-nitro-4-methoxybenzyl) amino-6-chloro quinazoline 1g, 4ml of acetic acids, 4ml of water, and the ethanol 40ml mixture gently, 1g was added small quantity every in the end of iron powder, and heating reflux was carried out for 2 hours. The insoluble matter of reaction mixture is filtered out, and the crystal which added concentrated hydrochloric acid to brown filtrate little by little, obtained yellow clear liquid, ice-cooled, and deposited is separated, and it dries, and is a 4-(3-amino-4-methoxybenzyl) amino-6-chloro quinazoline hydrochloride. 1.1g was obtained. This hydrochloride is dissolved in ethanol-water, and the crystal which added the sodium-hydroxide water solution little by little 15%, made it alkalinity, subsequently added water little by little, and was produced is separated, and it rinses, dries, and is 4-(3-amino-4-methoxybenzyl) amino-6-chloro quinazoline (aniline object). 770 mg was obtained. Next, 1ml of formic acid is dropped at 2ml of bottom acetic anhydrides of ice-cooling, and it heats for 15 minutes at 50 degrees C after that, ice-cools immediately, and is the above-mentioned aniline object to the mixture. 200mg was added with the crystal. By this **, subsequently it reacts at a room temperature for 1 hour, and the crystal which added water and was produced is separated, and it rinses, dries for 1 hour, and is a title compound. 130mg was obtained.
[0357] - Molecular formula ; C17H15N4O2Cl, yield (%);60 and melting point (degree-C);208 - 209, and Mass ; 343 (MH)+ and NMR delta (DMSO-d6); [3.82 (3H, s),] 4.68 (2H, d, J= 5.7Hz) 6.98 (1H, d, J= 8.2Hz), 7.09 (1H, dd, J= 2.0Hz, 8.2Hz) 7.71 (1H, d, J= 9.0Hz), 7.79 (1H, dd, J= 2.4Hz, 9.0Hz) 8.23 (1H, d, J= 2.0Hz), 8.27 (1H, d, J= 2.4Hz), 8.47 (2H, s), 8.88 (1H, t, J= 5.7Hz), 9.62 (1H, brs) example 544-(3-methanesulfonylamino-4-chloro benzyl) amino-6-chloro quinazoline [0358]
[Formula 138]
[0359] 4-(3-amino-4-chloro benzyl) amino-6-chloro quinazoline Methane sulfonyl chloride 75microl is added to mixture (100mg and pyridine 3ml), and it is 1.5 at a room temperature. Time amount stirring was carried out. The crystal which added 20ml of water to the reaction mixture little by little, and was produced is separated, and it rinses and dries, and is a title compound. 109mg was obtained.
[0360] - Molecular formula ; C16H14N4O2SCl2, yield (%);88 and melting point (degree-C);209 - 210, and Mass ; 397 (MH)+ and NMR delta (DMSO-d6); [3.01 (3H, s),] 4.75 (2H, d, J= 5.7Hz) 7.23 (1H, dd, J= 2.2Hz, 8.2Hz), 7.45 (1H, d, J= 8.2Hz) 7.46 (1H, d, J= 2.2Hz), 7.73 (1H, d, J= 9.0Hz) 7.81 (1H, dd, J= 2.4Hz, 9.0Hz), The following compounds were obtained according to the approach of 8.45 (1H, d, J= 2.4Hz), 8.47 (1H, s), 8.97 (1H, brt, J= 5.7Hz), and 55 to 9.4 (1H, brs) example 61 examples 51-54.
[0361] Example 554-(3-amino-4-hydroxybenzyl) amino - 6, 7, 8-trimethoxy quinazoline [0362]
[Formula 139]
[0363] - Molecular formula ; C18H20N4O4 and yield (%); quantitive and melting point (degree-C); amorphous Mass ; 357(M+H)+ and NMR delta (CDCl3); [3.68 (1H, brs),] 3.82 (1H, brs), 3.95 (3H, s), 4.02 (3H, s), 4.11 (3H, s) 4.68 (2H, d, J= 4.4Hz), 6.61 (1H, brs) 6.64 (1H, d, J= 7.6Hz), 6.77 (1H, d, J= 7.6Hz) 7.01 (1H, s), 8.50 (1H, brs), 8.60 (1H, s) example 564-(3-ethoxycarbonylamino-4-

ethoxycarbonyloxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0364]
[Formula 140]
[0365] - Molecular formula ; C24H28N4O8, yield (%);54, and melting point (degree-C);229 -230 (decomposition)
- Mass ; 501(M+H)+ and NMR delta (CDCl3); [1.31 (3H, t, J= 7.2Hz),] 1.40 (3H, t, J= 7.2Hz) 3.95 (3H, s), 4.03 (3H, s), 4.11 (3H, s), 4.21 (2H, q, J= 7.2Hz), 4.35 (2H, q, J= 7.2Hz) 4.81 (1H, d, J= 5.2Hz), 5.80 (1H, brt, J= 5.2Hz) 6.74 (1H, s), 6.87 (1H, s) 7.13 (1H, d, J= 8.0Hz), 7.20 (1H, d, J= 8.0Hz), 8.18 (1H, brs), 8.64 (1H, s) example 574-[benzoxazole-2(3H)-ON-5-ylmethyl] amino - 6, 7, 8-trimethoxy quinazoline [0366]
[Formula 141]
[0367] - Molecular formula ; C19H18N4O5, yield (%);62, and melting point (degree-C);232 -233 (decomposition)
- Mass ; 383(M+H)+ and NMR delta (DMSO-d6); [3.87 (3H, s),] 3.90 (3H, s), 3.96 (3H, s), 4.78 (2H, d, J= 5.6Hz), 7.06 (1H, s) 7.07 (1H, d, J= 8.0Hz), 7.20 (1H, d, J= 8.0Hz) 7.50 (1H, s), 8.35 (1H, s), 8.58 (1H, brt, J= 5.6Hz), 11.48 (1H, brs) example 584-(4-hydroxy-3-methanesulfonylamino benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0368]
[Formula 142]
[0369] - Molecular formula ; C19H22N4O6S, yield (%);56, and melting point (degree-C);215 -216 (decomposition)
- Mass ; 435(M+H)+ and NMR delta (DMSO-d6); [2.91 (3H, s),] 3.86 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 4.65 (2H, d, J= 5.6Hz) 6.83 (1H, d, J= 8.0Hz), 7.04 (1H, dd, J= 8.0Hz, 2.0Hz) 7.22 (1H, d, J= 2.0Hz), 7.50 (1H, s), 8.34 (1H, s), 8.52 (1H, brt, J= 5.6Hz), 8.66 (1H, brs), 9.75 (1H, brs) example 594-(3-amino-4-chloro benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0370]
[Formula 143]
[0371] - Molecular formula ; C18H19N4O3Cl, yield (%);86, and melting point (degree-C);181 -182 (decomposition)
- Mass ; 375(M+H)+ and NMR delta (CDCl3); [3.95 (3H, s),] 4.03 (3H, s), 4.08 (2H, brs), 4.13 (3H, s), 4.75 (2H, d, J= 5.6Hz) 5.65 (1H, brs), 6.67 (1H, s) 6.72 (1H, dd, J= 8.0Hz, 2.0Hz), 6.81 (1H, d, J= 2.0Hz), 7.23 (1H, d, J= 8.0Hz), 8.65 (1H, s) example 604-(4-chloro-3-formamide benzyl) amino - 6, 7, 8-trimethoxy quinazoline [0372]
[Formula 144]
[0373] - Molecular formula ; C19H19N4O4Cl, yield (%);68, and melting point (degree-C);202 -204 (decomposition)
- Mass ; 403(M+H)+ and NMR delta (DMSO-d6); [3.88 (3H, s),] 3.91 (3H, s), 3.98 (3H, s), 4.75 (2H, d, J= 5.6Hz), 7.14 (1H, dd, J= 8.4Hz, 2.0Hz) 7.42 (2H, d, J= 8.4Hz), 7.52 (1H, s) 8.15 (1H, d, J= 2.0Hz), 8.32 (1H, s), 8.35 (1H, s), 8.67 (1H, brs), 9.83 (1H, brs) example 614-(3-acetamido-4-chloro benzyl) amino-6-chloro quinazoline [0374]
[Formula 145]
[0375] - Molecular formula ; C17H14N4OCl2, yield (%);77 and melting point (degree-C);267 - 268, and Mass ; 361 (MH)+ and NMR delta (DMSO-d6); [2.06 (3H, s),] 4.74 (2H, d, J= 5.7Hz) 7.17 (1H, dd, J= 2.0Hz, 8.2Hz), 7.42 (1H, d, J= 8.2Hz) 7.69 (1H, brs), 7.72 (1H, d, J= 9.0Hz) 7.81 (1H, dd, J= 2.4Hz, 9.0Hz), 8.45 (1H, d, J= 2.4Hz) 8.46 (1H, s), 8.96 (1H, brt, J= 5.7Hz), 9.48 (1H, brs) example 624-(3, 4-dihydroxy benzyl) amino - 6, 7, 8-trimethoxy quinazoline Hydrochloride [0376]
[Formula 146]
[0377] 4-(3, 4-methylene dioxy benzyl) amino - 6, 7, and 8-trimethoxy quinazoline 2.00g (5.41 millimol) chloroform To 150ml solution, it is boron trichloride. 30ml of 1.0M methylene chloride solutions was dropped under room temperature stirring. After carrying out room temperature stirring for two days, the methanol was added, and bottom solvent distilling off of reduced pressure was carried out. After repeating this actuation 3 times, the silica gel column chromatography (chloroform-n-hexane) refined residue. Hydrochloric-acid-ethanol was added to the eluate, after bottom solvent distilling off of reduced pressure, ethanol was added, the crystal was separated and 0.59g of colorless needle shape crystals of a title compound was obtained.
[0378] - Molecular formula ; C18H19N3O5, HCl, yield (%);28, and melting point (degree-C);204 - 205 (decomposition)

- Mass ; 358(M+H)+ and NMR delta (DMSO-d6); [3.98 (3H, s),] 3.99 (3H, s), 3.99 (3H, s), 4.78 (2H, d, J= 5.6Hz), 6.65-7.71 (2H, m), 6.79 (1H, s), 7.94 (1H, s), 8.71 (1H, s), 8.90 (2H, brs), 10.54 (1H, brs), 14.06 (1H, brs) example 634-(3, 4-dihydroxy benzyl) amino-6-chloro quinazoline Hydrochloride [0379]
[Formula 147]
[0380] 4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinazoline 2.00g (6.37 millimol) chloroform To 150ml solution, it is boron trichloride. 40ml of 1.0M methylene chloride solutions was dropped under room temperature stirring. After carrying out room temperature stirring for two days, the methanol was added, and bottom solvent distilling off of reduced pressure was carried out. After repeating this actuation twice, precipitated crystal was washed with the methanol, it recrystallized from ethanol, and 1.53g of ****** of a title compound was obtained.
[0381] - Molecular formula ; C15H12N3O2 Cl-HCl, yield (%);71, and melting point (degree-C);154 -155 (decomposition)
- Mass ; 302(M+H)+ and NMR delta (DMSO-d6); [4.74 (2H, d, J= 5.6Hz),] 7.67 (1H, dd, J= 8.0Hz, 2.0Hz) 6.70 (1H, d, J= 8.0Hz), 6.81 (1H, d, J= 2.0Hz) 7.87 (1H, d, J= 8.8Hz), 8.02 (1H, dd, J= 8.8Hz, 2.0Hz) 8.76 (1H, d, J= 2.0Hz), 8.85 (1H, s) 8.90 (2H, brs), 10.42 (1H, brs) and molecular formula ; C21H25N5O5, yield (%);87, and melting point (degree-C); amorphous and Mass ; 428(M+H)+ and NMR delta (CDCl3); [1.44 (2H, s),] 2.93 (2H, t, J= 6.0Hz) 3.57 (2H, brs), 3.88 (3H, s), 4.00 (3H, s), 4.07 (3H, s), 4.70 (2H, d, J= 4.8Hz) 5.16 (1H, brs), 5.51 (1H, brs), 5.96 (2H, s), 6.56 (1H, s), 6.80 (1H, d, J= 8.0Hz), 6.86 (1H, d, J= 8.0Hz), 6.90 (1H, s) example 642-(3, 4-methylene dioxy benzyl) amino - 4, 6, 7, 8-tetramethoxy quinazoline [0382]
[Formula 148]
[0383] 2-chloro - 4, 6, 7, and 8-tetramethoxy quinazoline 1.00g (3.51 millimol), piperonyl amine 0.60g (3.97 millimol), and 0.60g of sodium carbonates are mixed to isopropyl alcohol 30ml, and heating reflux is carried out one whole day and night. Bottom solvent distilling off of reduced pressure of the reaction mixture was carried out, the silica gel column chromatography (ethyl-acetate-n-hexane) refined residue, and 0.12g of oil of a title compound was obtained.
[0384] - Molecular formula ; C20H21N3O6, yield (%);9, and melting point (degree-C); oil and NMR delta (CDCl3); [3.91 (3H, s),] 4.02 (3H, s) 4.04 (6H, s) 4.63 (2H, d, J= 6.0Hz), 5.30 (1H, brs) 5.93 (2H, s) 6.75 (1H, d, J= 8.0Hz) 6.86 (1H, dd, J= 8.0Hz, 1.6Hz) 6.92 (1H, d, J= 1.6Hz) 7.06 (1H, s)
Example 652-chloro - 4, 6, 7, 8-tetramethoxy quinazoline [0385]
[Formula 149]
[0386] 2, 4-dichloro - It is a methanol about 6, 7, and 8-trimethoxy quinazoline 5.00g (17.3 millimol). 100ml is made to suspend and it is sodium hydride. Heating reflux is carried out after adding 1.5g gradually. Vacuum concentration of the reaction mixture was carried out several hours after, water was added, precipitated crystal was separated, and it washed with water, and it was air-dry and 4.80g of light ****** of a title compound was obtained.
[0387] - Yield (%);97 and melting point (degree-C);119 - 120, and Mass ; 285(M+1)+ and NMR delta (CDCl3); [3.98 (3H, s),] 4.06 (3H, s), 4.12 (3H, s), 4.19 (3H, s), example of 7.17 (1H, s) reference 62-(4-carboxy piperidino)-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinazoline [0388]
[Formula 150]
[0389] They are ethanol 10ml, 5ml of water, and a sodium hydroxide to 2-(4-ethoxycarbonyl piperidino)-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinazoline 1g. 820mg was added and it flowed back for 20 minutes. After carrying out vacuum concentration of the solvent, 1-N hydrochloric acid is added and it neutralizes, and the depositing crystal is separated, and it is a title compound. 920mg was obtained.
[0390] - Molecular formula ; C22H21N4O4Cl, yield (%);98 and melting point (degree-C);221 - 222, and Mass m/e ; 441 (M+1) and NMR delta (DMSO-d6); [1.38 (2H, m),] 1.80 (2H, dd, J= 13.2Hz, 2.4Hz) 2.48 (1H, m), 2.96 (2H, t, J= 12.0Hz) 4.54 (2H, d, J= 5.6Hz), 4.56 (2H, dt, J= 12.0Hz, 3.2Hz) 5.94 (2H, s), 6.81 (1H, d, J= 8.0Hz) 6.84 (1H, d, J= 8.0Hz), 6.93 (1H, s) 7.24 (1H, d, J= 9.2Hz), 7.46 (1H, dd, J= 9.2Hz, 2.0Hz), 8.13 (1H, d, J= 2.0Hz), 8.55 (1H, t, J= 5.6Hz) example 662-benzyloxymethyl-4-chloro-6-methoxy quinazoline [0391]
[Formula 151]

[0392] 2 - 30ml of phosphorus oxychloride is added to benzyloxymethyl-6-methoxy quinazoline-4(3H)-ON 1.50g (5.06 millimol) acetonitrile 75ml suspension, and heating reflux is carried out. Bottom solvent distilling off of reduced pressure of the reaction mixture is carried out 1 hour after, the residue obtained is dissolved in chloroform, and it washes with saturation sodium bicarbonate water. An organic layer is filtered after desiccation with sulfuric anhydride magnesium, and bottom solvent distilling off of reduced pressure of the filtrate is carried out. The silica gel column chromatography (ethyl-acetate-n-hexane) refined residue, and 1.10g of ****** of a title compound was obtained.
[0393] - Yield (%);69 and melting point (degree-C);49 - 50, and Mass ; 315(M+1)+ and NMR delta (CDCl3); [3.98 (3H, s),] 4.79 (2H, s), 4.84 (2H, s), 7.42 (1H, d, J= 2.8Hz), The following compounds were obtained according to the approach of 7.26-7.46 (5H, m), 7.57 (1H, dd, J= 9.2Hz, 2.8Hz), 8.01 (1H, d, J= 9.2Hz) examples 67 - the example 6 of 70 reference.
[0394] An example 672, 6-dichloro-4-(3, 4-methylene dioxy benzyl) oxy-quinazoline [0395]
[Formula 152]
[0396] - Molecular formula ; C16H10Cl2N2O3, yield (%);55 and melting point (degree-C);141 - 142, and Mass m/e ; 349 (M+1) and NMR delta (CDCl3); [5.54 (2H, s),] 6.01 (2H, s) 6.86 (1H, d, J= 8.8Hz), 7.01 (1H, d, J= 8.8Hz) 7.02 (1H, s), 7.76 (1H, dd, J= 8.0Hz, 2.4Hz) 7.81 (1H, dd, J= 8.0Hz, 0.8Hz), 8.09 (1H, dd, J= 2.4Hz, 0.8Hz) example 682-(4-carboxy piperidino)-4-(3, 4-methylene dioxy benzyl) oxy--6-chloro quinazoline [0397]
[Formula 153]
[0398] - Molecular formula ; C22H20ClN3O5, yield (%);84 and melting point (degree-C);145 - 147, and Mass m/e ; 442 (M+1) and NMR delta (DMSO-d6); [1.47 (2H, m),] 1.88 (2H, m), 2.49 (1H, m), 3.10 (2H, brt, J= 13.2Hz), 4.60 (2H, brd, J= 13.2Hz) 5.43 (2H, s), 6.01 (2H, s) 6.91 (1H, d, J= 8.0Hz), 7.02 (1H, d, J= 8.0Hz) 7.11 (1H, s), 7.39 (1H, d, J= 8.8Hz), 7.61 (1H, dd, J= 8.8Hz, 2.4Hz), 7.77 (1H, d, J= 2.4Hz) examples 692, 6-dichloro-4-(3, 4-methylene dioxy benzyl) thio quinazoline [0399]
[Formula 154]
[0400] - Molecular formula ; C16H10Cl2N2O2S, yield (%);92 and melting point (degree-C);180 - 182, and Mass m/e ; 365 (M+1) and NMR delta (CDCl3); [4.55 (2H, s),] 5.96 (2H, s) 6.77 (1H, d, J= 8.4Hz), 6.96 (1H, s) 6.96 (1H, d, J= 8.4Hz), 7.77 (1H, dd, J= 8.8Hz, 2.0Hz) 7.82 (1H, d, J= 8.8Hz), 7.99 (1H, d, J= 2.0Hz) example 702-(4-carboxy piperidino)-4-(3, 4-methylene dioxy benzyl) thio-6-chloro quinazoline [0401]
[Formula 155]
[0402] - Molecular formula ; C22H20ClN3O4S, yield (%);98 and melting point (degree-C);153 - 154, and Mass m/e ; 458 (M+1) and NMR delta (DMSO-d6); [1.50 (2H, m),] 1.82 (2H, m), 2.39 (1H, brs), 3.18 (2H, m), 4.48 (2H, s), 4.55 (2H, brs), 5.96 (2H, s), 6.82 (1H, d, J= 8.0Hz) 6.92 (1H, d, J= 8.0Hz), 6.99 (1H, s), 7.41 (1H, brd, J= 8.8Hz), 7.62 (1H, brd, J= 8.8Hz), 7.69 (1H, brs) examples 712, a 6-dichloro-4-(3, 4-methylene dioxy benzyl) amino quinoline [0403]
[Formula 156]
[0404] a) 2, 4, and 6-TORIKURORO quinoline 5-chloro anthranilic-acid methyl ester was left, and the title compound was obtained by Journal of American Chemical Society, 68 volumes, and the same approach as 1285 pages (1946).
[0405] - NMR delta (CDCl3); [7.55 (1H, s) 7.74 (1H, dd, J= 9.0Hz, 2.2Hz),] 7.98 (1H, d, J= 9.0Hz) 8.19 (1H, d, J= 2.2Hz)b Compound obtained by the 2 and 6-dichloro-4-(3, 4-methylene dioxy benzyl) amino quinoline a 500mg, 3, 4-methylene dioxy benzylamine 350mg, N, and N-diisopropyl ethylamine 1ml and mixture of 4ml of N-methyl-2-pyrrolidones It was made to react among a 130-degree C oil bath for 10 hours. Water was added to reaction mixture, ethyl acetate extracted, and the ethyl acetate layer was washed with water and saturation brine, and was dried and condensed with sulfuric anhydride magnesium. Residue is given to a silica gel column chromatography (5 - 20% ethyl acetate / hexane), and it is a title compound as a high polarity component. 430mg was obtained.
[0406] - Molecular formula ; C17H12Cl2N2O3 and melting point (degree-C);198 - 199 ** and Mass m/e ; 347 (M+1) and NMR delta (CDCl3); [4.39 (2H, d, J= 4.9Hz),] 5.21 (1H, t, J= 4.9Hz) 6.00 (2H, s), 6.47 (1H, s), 6.82-6.87 (3H, m), 7.58 (1H, dd, J= 9.0Hz, 2.2Hz), It is a 4 and 6-

dichloro-2-(3, 4-methylene dioxy benzyl) amino quinoline as a low polar component to 7.65 (1H, d, J= 2.2Hz) and 7.84 (1H, d, J= 9.0Hz) coincidence. 190mg was obtained.
[0407] - NMR delta (CDCl3); [4.58 (2H, d, J= 5.7Hz),] 5.00 (1H, brt, J= 5.7Hz) 5.94 (2H, s), 6.74 (1H, s) 6.77 (1H, d, J= 7.9Hz), 6.84 (1H, dd, J= 7.9Hz, 1.6Hz) 6.88 (1H, d, J= 1.6Hz), 7.50 (1H, dd, J= 9.0Hz, 2.4Hz), 7.62 (1H, d, J= 9.0Hz), 7.96 (1H, d, J= 2.4Hz) examples 722, a 6-dichloro-4-(3-chloro-4-methoxybenzyl) amino quinoline [0408]
[Formula 157]
[0409] The title compound was obtained according to the approach of an example 71.
[0410] - Molecular formula ; C17H13Cl3N2O, yield (%);59 and melting point (degree-C);204 - 205, and NMR delta (CDCl3); [3.91 (3H, s),] 3.40 (3H, s) 4.38 (2H, d, J= 5.1Hz), 4.97 (1H, t, J= 5.1Hz) 5.93 (1H, s), 6.93 (1H, d, J= 8.4Hz) 7.24 (1H, dd, J= 8.4Hz, 2.2Hz), 7.40 (1H, d, J= 2.2Hz) 7.50 (1H, dd, J= 8.8Hz, 2.2Hz), 7.59 (1H, d, J= 2.2Hz) 7.71 (1H, d, J= 8.8Hz) example 732-(4-carboxy piperidino)-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinoline [0411]
[Formula 158]
[0412] a) The 2-(4-ethoxycarbonyl piperidino)-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinoline 2, 6-dichloro-4-(3, 4-methylene dioxy benzyl) amino quinoline 130mg, isonipecotic acid ethyl ester 500microl and mixture of 1ml of N-methyl-2-pyrrolidones It heated among the 150-degree C oil bath for 3 hours. Water was added after cooling reaction mixture, ethyl acetate extracted, and after washing an ethyl acetate layer with water and saturation brine, it was dried and condensed with sulfuric anhydride magnesium. A silica gel column chromatography (20 - 50% ethyl acetate / hexane) refines residue, and it is a title compound. 150mg was obtained.
[0413] - NMR delta (CDCl3); [1.26 (3H, t, J= 7.1Hz),] 1.70-1.81 (2H, m), 1.95-2.02 (2H, m), 2.54 (1H, tt, J= 11.2Hz, 3.8Hz) 2.97-3.06 (2H, m), 4.14 (2H, q, J= 7.1Hz), 4.32-4.39 (4H, m), 4.86 (1H, t, J= 5.5Hz) 5.98 (3H, s), 6.81 (1H, d, J= 7.7Hz) 6.84-6.89 (2H, m), 7.39 (1H, dd, J= 9.0Hz, 2.4Hz) 7.47 (1H, d, J= 2.4Hz), Compound obtained by 7.55(1H, d, J= 9.0Hz) b2-(4-carboxy piperidino)-4-(3, 4-methylene dioxy benzyl) amino-6-chloro quinoline a 150mg, 1ml of 1-N sodium-hydroxide water solutions and ethanol 10ml mixture were heated among the 60-degree C oil bath for 2 hours. It is 130mg of title compounds by separating the crystal which condensed reaction mixture, added water, added 1ml of 1 moreN hydrochloric acids, neutralized, and was produced, and rinsing and drying. It obtained.
[0414] - Molecular formula ; C23H22ClN3O4, yield (%);92 and melting point (degree-C);235 - 237, and Mass m/e ; 440 (M+1) and NMR delta (DMSO-d6); [1.37-1.50 (2H, m),] 1.77-1.86 (2H, m), 2.89-3.00 (2H, br, 3 peak), 4.20-4.28 (2H, br, 2 peak), 4.42 (2H, d, J= 5.7Hz), 5.96 (2H, s), 5.97 (1H, s), 6.85 (1H, d, J= 7.9Hz), 6.92 (1H, dd, J= 7.9Hz, 1.5Hz) 6.98 (1H, d, J= 1.5Hz), 7.42 (2H, brs), 7.58 (1H, brs), 8.15 (1H, brs) example 742-(4-carboxy piperidino)-4-(3-chloro-4-methoxybenzyl) amino-6-chloro quinoline [0415]
[Formula 159]
[0416] The title compound was obtained according to the approach of an example 73.
[0417] - Molecular formula ; C23H23Cl2N3O3 and melting point (degree-C);282 - 283, and Mass m/e ; 460 (M+1) and NMR delta (DMSO-d6); [1.36-1.48 (2H, m),] 1.76-1.84 (2H, m), 2.43-2.53 (1H, m), 2.91 (2H, t, J= 11.2Hz) 4.26 (2H, brd, J= 13.2Hz), 4.44 (2H, d, J= 5.9Hz) 5.97 (1H, s), 7.10 (1H, d, J= 8.6Hz) 7.36 (1H, dd, J= 8.6Hz, 2.2Hz), 7.38 (2H, s), 7.50 (2H, brs and d, J= 2.2Hz), 8.11 (1H, s) example 752-methoxy-4-(3-chloro-4-methoxybenzyl) amino-6-chloro quinoline [0418]
[Formula 160]
[0419] 2, 6-dichloro-4-(3-chloro-4-methoxybenzyl) amino quinoline 200mg, methanol 0.5ml, potassium t-butoxide The heating reflux of the mixture (200mg and 1,4-dioxane 3ml) was carried out for 1 hour. Water was added after cooling reaction mixture, ethyl acetate extracted, and the ethyl acetate layer was washed with saturation brine, and was condensed after desiccation with sulfuric anhydride magnesium. It recrystallizes [hexane / ethyl-acetate-] after purification with a silica gel column chromatography (10 - 30% ethyl acetate / hexane), and is a title compound. 150mg was obtained.
[0420] - Molecular formula ; C18H16Cl2N2O2, yield (%);76 and melting point (degree-C);170 - 171, and NMR delta (CDCl3); [3.93 (3H, s),] 4.42 (2H, d, J= 5.2Hz) 5.22 (1H, t, J= 5.2Hz), 6.46 (1H, s) 6.96 (1H, d, J= 8.4Hz), 7.25 (1H, dd, J= 8.4Hz, 2.2Hz) 7.41 (1H, d, J= 2.2Hz), 7.59 (1H, dd,

J= 9.0Hz, 2.2Hz) 7.66 (1H, d, J= 2.2Hz), 7.85 (1H, d, J= 9.0Hz) example 762-(3, 4-methylene dioxy benzyl) amino-4-(4-carboxy piperidino)-6-chloro quinoline [0421]
[Formula 161]
[0422] 4, the 6-dichloro-2-(3, 4-methylene dioxy benzyl) amino quinoline which carried out the byproduction by b of an example 71 The same actuation as an example 73 is performed using 140mg, and it is a title compound. 130mg was obtained.
[0423] - Molecular formula ; C23H22ClN3O4, yield (%);99 and melting point (degree-C);270 - 272, and Mass m/e ; 440 (M+1) and NMR delta (DMSO-d6); [1.78-1.89 (2H, m),] 1.96-2.04 (2H, m), 2.70-2.79 (2H, m), 3.26-3.36 (2H, m), 4.49 (2H, d, J= 5.7Hz), 5.96 (2H, s), 6.37 (1H, s), 6.85 (2H, s), 6.94 (1H, s) 7.37 (1H, t, J= 5.7Hz), 7.41 (1H, dd, J= 8.8Hz, 2.4Hz), 7.46 (1H, d, J= 8.8Hz), 7.60 (1H, d, J= 2.4Hz) example 772-chloro-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline [0424]

[Formula 162]
[0425] a) 4 - Hydroxyquinoline-2-ON-6-carboxylic-acid 4-aminobenzene -1 and 4-dicarboxylic acid dimethyl ester were left, and the title compound was obtained by Journal of American Chemical Society, 68 volumes, and the same actuation as 1285 pages (1946).
[0426] - NMR delta (DMSO-d6); [5.79 (1H, s) 7.31 (1H, d, J= 8.6Hz),] 8.02 (1H, dd, J= 8.6Hz, 2.0Hz) 8.39 (1H, d, J= 2.0Hz), 11.51 (1H, s), 11.63 (1H, brs), 12.86(1H, brs) b The heating reflux of 9g of compounds and the mixture of 50ml of phosphorus oxychloride which were obtained by the 2 and 4-dichloro quinoline-6-carboxamide a was carried out for 1 hour. It poured slowly, having condensed reaction mixture, having added the ethyl-acetate-acetone to residue, having considered as the suspension of homogeneity, and stirring in the ice-cooled dark aqueous ammonia. After separating the depositing crystal after 30 minutes and washing with water and ethyl acetate, it dried and 8.96g of title compounds was obtained.
[0427] - NMR delta (DMSO-d6); [7.72 (1H, brs),] 8.06 (1H, s) 8.10 (1H, d, J= 8.8Hz), 8.34 (1H, dd, J= 8.8Hz, 2.0Hz) 8.43 (1H, brs), 8.73(1H, d, J= 2.0Hz) c 3g of compounds, the lithium chloride which were obtained by the 2 and 4-dichloro-6-cyano quinoline b The heating reflux of 300mg and the mixture of 30ml of phosphorus oxychloride was carried out for 2 hours. Reaction mixture is condensed and it is benzene. 120ml was added, it washed in the saturation sodium-hydrogencarbonate water solution, the benzene layer was washed with saturation brine, and it dried with sulfuric anhydride magnesium, and through the silica gel bed, after filtration, silica gel was further set [it washed it and] and condensed with benzene, ******ed residue from the ethyl-acetate-hexane, and obtained 2.15g of title compounds.
[0428] - NMR delta (CDCl3); [7.65 (1H, s) 7.95 (1H, dd, J= 8.8Hz, 1.8Hz),] 8.14 (1H, d, J= 8.8Hz) 8.60 (1H, d, J= 1.8Hz)d 1g of compounds obtained by 2-chloro-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline c, 3-chloro-4-methoxy benzylamine 1g [of hydrochlorides], N, and N-diisopropyl ethylamine 2.4ml and mixture of 10ml of N-methyl-2-pyrrolidones It was made to heat and react with 130-degree-C oil bath for 1 hour. It dries, after separating the crystal which added water and ethyl acetate after the cold and was produced and washing with water and ethyl acetate, and it is 610mg of title compounds. It obtained.
[0429] - Molecular formula ; C18H13Cl2N3O, yield (%);38 and melting point (degree-C);254 - 255, and NMR delta (CDCl3); [3.94 (3H, s),] 4.45 (2H, d, J= 4.9Hz) 5.41 (1H, d, J= 4.9Hz), 6.54 (1H, s) 6.98 (1H, d, J= 8.4Hz), 7.26 (1H, dd, J= 8.4Hz, 2.2Hz) 7.41 (1H, d, J= 2.2Hz), 7.80 (1H, dd, J= 8.8Hz, 1.6Hz) 7.97 (1H, d, J= 8.8Hz), 8.08 (1H, d, J= 1.6Hz) example 782-(4-carboxy piperidino)-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline [0430]
[Formula 163]
[0431] a) 2-(4-ethoxycarbonyl piperidino)-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline 2-chloro-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline 750mg, isonipecotic acid 1.6ml and mixture of 5ml of N-methyl-2-pyrrolidones It heated among 130-degree-C oil bath for 3 hours. Water was added to reaction mixture after the cold, ethyl acetate extracted, and after washing an ethyl acetate layer with water and saturation brine, it was dried and condensed with sulfuric anhydride magnesium. Residue is given to a silica gel column chromatography (20 - 40% ethyl acetate / hexane), and subsequently it recrystallizes [hexane / ethyl-acetate-], and is a title compound. 860mg was obtained.

[0432] - NMR delta (CDCl3); [1.26 (3H, t, J= 7.1Hz),] 1.68-1.79 (2H, m), 1.95-2.03 (2H, m), 2.58 (1H, tt, J= 11.0Hz, 4.0Hz) 3.03-3.12 (2H, m), 3.92 (3H, s) 4.15 (2H, q, J= 7.1Hz), 4.36-4.43 (4H, m), 5.08 (1H, t, J= 5.1Hz), 5.94 (1H, s) 6.95 (1H, d, J= 8.4Hz), 7.26 (1H, dd, J= 8.4Hz, 2.2Hz) 7.42 (1H, d, J= 2.2Hz), 7.55-7.61 (2H, m), 7.88(1H, s) b Compound obtained by 2-(4-carboxy piperidino)-4-(3-chloro-4-methoxybenzyl) amino-6-cyano quinoline a 500mg, Mixture (2ml [of 1N sodium-hydroxide water solutions] and tetrahydrofuran 20ml and ethanol 25ml) was made to react at 50 degrees C for 2 hours. If 2ml of 1-N hydrochloric acids is added and about about 20ml is distilled off, the crystal has deposited. It dries, after separating this crystal and washing with water and ethyl acetate, and it is a title compound. 460mg was obtained.

[0433] - Molecular formula ; C24H23ClN3O3, yield (%);98, and melting point (degree-C);274 -276 (decomposition)

- NMR delta (DMSO-d6); [1.35-1.47 (2H, m),] 1.78-1.87 (2H, m), 2.47-2.56 (1H, m), 2.95-3.04 (2H, m), 3.81 (3H, s), 4.30-4.39 (2H, m), 4.46 (2H, d, J= 5.7Hz) 6.01 (1H, s), 7.11 (1H, d, J= 8.6Hz) 7.37 (1H, dd, J= 8.6Hz, 2.2Hz), 7.40 (1H, d, J= 8.8Hz) 7.52 (1H, d, J= 2.2Hz), 7.65 (1H, dd, J= 8.8Hz, 1.6Hz) 7.68 (1H, t, J= 5.7Hz), pyrid [8.55 (1H, d, J= 1.6Hz) and 12.20 (1H, brs) example 792-chloro-8-(3, 4-methoxy dioxy benzyl) amino] [2 and 3-d] pyrimidine [0434]

[Formula 164]

[0435] 2 and 8-dichloro pyrid [2 and 3-d] pyrimidine Triethylamine 66mg and piperonyl amine 89mg were added to 118mg 20ml tetrahydrofuran solution, and it stirred at the room temperature for 16 hours. The crystal which added water and deposited is separated and it is 166mg of title compounds. It obtained.

[0436] - Molecular formula ; C15H11ClN4O2, yield (%);89 and melting point (degree-C);200 - 202, and Mass m/e ; 315 (M+1) and NMR delta (DMSO-d6); [4.64 (1H, d, J= 5.6Hz) 5.97 (2H, s),] 6.85 (1H, d, J= 8.0Hz) 6.87 (1H, d, J= 8.0Hz), 6.96 (1H, s) 7.55 (1H, dd, J= 8.0Hz, 4.4Hz), 8.73 (1H, dd, J= 8.0Hz, 1.6Hz) 8.96 (1H, dd, J= 4.4Hz, 1.6Hz), 9.46 (1H, t, J= 5.6Hz) example 802-(4-carboxy piperidino)-8-(3, 4-methylene dioxy benzyl) amino [2 and 3-pyrid d] pyrimidine [0437]

[Formula 165]

[0438] a) 2-(4-ethoxycarbonyl piperidino)-8-(3, 4-methylene dioxy benzyl) amino [2 and 3-pyrid d] pyrimidine [0439]

[Formula 166]

[0440] 2-chloro-8-(3, 4-methylene dioxy benzyl) amino pyrid [2 and 3-d] pyrimidine They are triethylamine 41mg and isonipecotic acid ethyl 190mg to 127mg 8ml tetrahydrofuran solution. In addition, it flows back for 2 hours. Water was added to reaction mixture, under chloroform, it extracted twice, and the doubled organic layer was dried with magnesium sulfate, and solvent distilling off was carried out. A silica gel column chromatography (ethyl acetate) refines residue, and it is a title compound. 175mg (yield 100%) was obtained.

[0441] b) 2-(4-carboxy piperidino)-8-(3, 4-methylene dioxy benzyl) amino [2 and 3-pyrid d] pyrimidine [0442]

[Formula 167]

[0443] The 2-(4-ethoxycarbonyl piperidino)-8-(3, 4-methylene dioxy benzyl) amino [2 and 3-pyrid d] pyrimidine 1.56ml of 1-N sodium hydroxides was added to 170mg 10ml ethanol solution, and it stirred at the room temperature for 6 hours. The crystal which deposited after adding 1-N hydrochloric acid and water and neutralizing is separated, and it is a title compound. 121mg was obtained.

[0444] - Molecular formula ; C21H21N5O4, yield (%);76 and melting point (degree-C);255 - 256, and Mass m/e ; 408 (M+1) and NMR delta (DMSO-d6); [1.39 (2H, m),] 1.80 (2H, m) 2.51 (1H, m) 3.01 (2H, brt, J= 11.2Hz), 4.56 (2H, d, J= 5.6Hz) 4.61 (2H, brd, J= 12.8Hz), 5.94 (2H, s) 6.82 (1H, d, J= 8.0Hz), 6.84 (1H, d, J= 8.0Hz) 6.93 (1H, s), 7.03 (1H, dd, J= 8.0Hz, 4.4Hz) 8.38 (1H, dd, J= 8.0Hz, 1.6Hz) 8.61 (1H, dd, J= 4.4Hz, 1.6Hz) 8.70 (1H, t, J= 5.6Hz) 12.16 (1H, brs)

Example 815-chloro-2-methane sulfonyl-1-(3, 4-methylene dioxy benzyl) benzimidazole [0445]

[Formula 168]

[0446] It is dimethylformamide about 6-chloro-2-mercaptobenzimidazole 8.89g. It dissolved in 150ml, 6.65g of potassium carbonate and 6.15g of methyl iodides were added under ice-cooling, and it stirred for 50 minutes by this **. Water was added and ethyl acetate extracted. It

condensed under reduced pressure after desiccation, and the rough 6-chloro-2-methylthio benzimidazole was obtained.
[0447] The rough purification object obtained in the top was dissolved in 100ml of methylene chlorides, m-CPBA 17.3g was added under ice-cooling 80%, and overnight stirring was carried out at the room temperature. 7g of sodium thiosulfates was added, it stirred for 30 minutes at the room temperature, and water was added. The organic layer was isolated preparatively, after desiccation, the silica gel column chromatography was given and 6-chloro-2-methane sulfonyl benzimidazole 10g was obtained.
[0448] 6-chloro-2-methane sulfonyl benzimidazole 2.3g is dissolved in dimethylformamide 30ml, and it is bottom 60% sodium hydride of ice-cooling. 480mg and piperonyl chloride 2.04g were added, and it heated at 80 degrees C for 4 hours. At the room temperature, insoluble matter was filtered out after overnight neglect and it condensed under reduced pressure. The silica gel column chromatography was given and the title compound was obtained.
[0449] - Molecular formula ; C16H13ClN2O4S, yield (%);25 and melting point (degree-C);129 - 131, and Mass m/e ; 365 (MH+) and NMR delta (CDCl3); [3.48 (3H, s),] 5.64 (2H, s), 5.91 (2H, s), 6.73-6.76 (3H, m), 7.27 (1H, d, J= 8.8Hz) 7.31 (1H, dd, J= 8.8Hz, 2.0Hz), 7.80 (1H, d, J= 2.0Hz) example 826-chloro-2-methane sulfonyl-1-(3, 4-methylene dioxy benzyl) benzimidazole [0450]
[Formula 169]
[0451] It sets in the example 81 and is 5. - The title compound was obtained by being further eluted after chloro-2-methane sulfonyl-1-(3, 4-methylene dioxy benzyl) benzimidazole elution.
[0452] - Molecular formula ; C16H13ClN2O4S, yield (%);22 and melting point (degree-C);140 - 142, and Mass m/e ; 365 (MH+) and NMR delta (CDCl3); [3.48 (3H, s),] 5.62 (2H, s), 5.93 (2H, s), 6.73-6.77 (3H, m), 7.32 (1H, d, J= 8.4Hz), 7.33 (1H, d, J= 1.2Hz), 7.74 (1H, dd, J= 8.4Hz, 1.2Hz) example 835-chloro-2-methoxy-1-(3, 4-methylene dioxy benzyl) benzimidazole [0453]
[Formula 170]
[0454] mixture of the 5-chloro-2-sulfonyl methyl-1-(3, 4-methylene dioxy benzyl) benzimidazole and the 6-chloro-2-sulfonyl methyl-1-(3, 4-methylene dioxy benzyl) benzimidazole 448mg is dissolved in methanol 20ml, and sodium-methoxide 10ml is added 28% — heating reflux was carried out for 1.5 hours. It ice-cooled, the hydrochloric acid neutralized 10%, and ethyl acetate extracted. It condensed under reduced pressure after desiccation, the silica gel column chromatography was given, and the title compound was obtained.
[0455] - Molecular formula ; C16H13ClN2O3, yield (%);31 and melting point (degree-C);117 - 118, and Mass m/e ; 317 (MH+) and NMR delta (CDCl3); [4.21 (3H, s),] 5.01 (2H, s), 5.92 (2H, s), 6.65 (1H, d, J= 1.6Hz), 6.68 (1H, dd, J= 8.0Hz, 1.6Hz) 6.73 (1H, d, J= 8.0Hz), 6.96 (1H, d, J= 8.4Hz), 7.05 (1H, dd, J= 8.4Hz, 2.0Hz), 7.51 (1H, d, J= 2.0Hz) example 846-chloro-2-methoxy-1-(3, 4-methylene dioxy benzyl) benzimidazole [0456]
[Formula 171]
[0457] an example 83 — setting — 5 — the title compound was obtained by being further eluted after - chloro-2-methoxy-1-(3, 4-methylene dioxy benzyl) benzimidazole elution.
[0458] - Molecular formula ; C16H13ClN2O3, yield (%);26 and melting point (degree-C);133 - 134, and Mass m/e ; 317 (MH+) and NMR delta (CDCl3); [4.21 (3H, s),] 4.99 (2H, s), 5.92 (2H, s), 6.65 (1H, d, J= 1.6Hz), 6.68 (1H, dd, J= 8.0Hz, 1.6Hz) 6.74 (1H, d, J= 8.0Hz), The following compounds were obtained according to the approach of 7.05 (1H, d, J= 1.6Hz), 7.10 (1H, dd, J= 8.8Hz, 1.6Hz), and 85 to 7.43 (1H, d, J= 8.8Hz) example 98 examples 81-84.
[0459] Example 851-(3, 4-methylene dioxy benzyl) benzimidazole [0460]
[Formula 172]
[0461] - Molecular formula ; C15H12N2O2, yield (%);34 and melting point (degree-C);107 - 108, and Mass m/e ; 253 (MH+) and NMR delta (CDCl3); [5.23 (2H, s),] 5.92 (2H, s) 6.63 (1H, d, J= 1.6Hz), 6.70 (1H, dd, J= 8.0Hz, 1.6Hz) 6.76 (1H, d, J= 8.0Hz), 7.23-7.32 (3H, m), 7.80-7.83 (1H, m), 7.92 (1H, s) example 861-(2-propoxy benzyl) benzimidazole [0462]
[Formula 173]
[0463] - Molecular formula ; C17H18N2O, yield (%);89 and melting point (degree-C);85 - 86, and Mass m/e ; 267 (MH+) and NMR delta (CDCl3); [1.02 (3H, t, J= 7.4Hz),] 1.78-1.86 (2H, m), 3.95 (2H, t, J= 6.6Hz), 5.35 (2H, s), 6.86-6.90 (2H, m), 7.06-7.09 (1H, m), 7.23-7.28 (3H, m), 7.40-7.43

(1H, m), 7.79-7.82 (1H, m), 7.99 (1H, s) example 872-(3, 4-methylene dioxy benzyl) benzimidazole [0464]
[Formula 174]
[0465] - Molecular formula ; C15H12N2O2, yield (%);62 and melting point (degree-C);143 - 146, and Mass m/e ; 253 (MH+) and NMR delta (DMSO-d6); [4.43 (2H, s),] 5.99 (2H, s), 6.89-6.94 (2H, m), 7.09 (1H, s), 7.48-7.52 (2H, m), 7.72-7.76 (2H, m) example 881-(3, 4-methylene dioxy benzyl)-6-methoxy benzimidazole [0466]
[Formula 175]
[0467] - Molecular formula ; C16H14N2O3, yield (%);70 and melting point (degree-C);134 - 135, and Mass m/e ; 283(M+1)+ and NMR delta (CDCl3); [3.82 (3H, s),] 5.21 (2H, s) 5.95 (2H, s) 6.64 (1H, d, J= 1.8Hz), 6.71 (1H, dd, J= 7.6Hz, 1.8Hz) 6.75 (1H, d, J= 2.4Hz), 6.78 (1H, d, J= 7.6Hz) 6.93 (1H, dd, J= 8.8Hz, 2.4Hz) 7.70 (1H, d, J= 8.8Hz) 7.90 (1H, s)
Example 891-(2-chloro -4, 5-methylene dioxy benzyl)-6-methoxy benzimidazole [0468]
[Formula 176]
[0469] - Molecular formula ; C16H13ClN2O3, yield (%);81 and melting point (degree-C);108 - 109, and Mass m/e ; 317(M+1)+ and NMR delta (CDCl3); [3.84 (3H, s),] 5.322 (2H, s), 5.97 (2H, s), 6.40 (1H, s), 6.80 (1H, s), 6.91 (1H, s), 6.95 (1H, d, J= 8.8Hz), 7.72 (1H, d, J= 8.8Hz), 7.96 (1H, s) example 901-[2-(3, 4-methylenedioxyphenyl) ethyl]-6-methoxy benzimidazole [0470]
[Formula 177]
[0471] - Molecular formula ; C17H16N2O3, yield (%);69, and melting point (degree-C); oil and Mass m/e ; 297(M+1)+ and NMR delta (CDCl3); [3.04 (2H, t, J= 6.8Hz),] 3.87 (3H, s) 4.31 (2H, t, J= 6.8Hz), 5.93 (2H, s) 6.43 (1H, dd, J= 8.0Hz, 2.0Hz), 6.52 (1H, d, J= 2.0Hz) 6.68 (1H, d, J= 8.0Hz), 6.77 (1H, d, J= 2.4Hz) 6.92 (1H, dd, J= 8.8Hz, 2.4Hz), 7.57 (1H, s), 7.67 (1H, d, J= 8.8Hz) example 916-chloro-1-(3, 4-methylene dioxy benzyl) benzimidazole [0472]
[Formula 178]
[0473] - Molecular formula ; C15H11ClN2O2 and melting point (degree-C);122 - 123, and Mass m/e ; 287 (MH+) and NMR delta (CDCl3); [5.18 (2H, s),] 5.94 (2H, s) 6.61 (1H, d, J= 1.2Hz), 6.68 (1H, dd, J= 8.0Hz, 1.2Hz) 6.77 (1H, d, J= 8.0Hz), 7.22- the 7.40 (2H, m), 7.71 (1H, d, J= 8.8Hz), and 7.90 (1H, s) example 925-chloro-1-(3, 4-methylene dioxy benzyl) benzimidazole [0474]
[Formula 179]
[0475] - Molecular formula ; C15H11ClN2O2, yield (%);83 and melting point (degree-C);113 - 114, and Mass m/e ; 287 (MH+) and NMR delta (CDCl3); [5.20 (2H, s),] 5.93 (2H, s) 6.60 (1H, d, J= 1.6Hz), 6.67 (1H, dd, J= 7.6Hz, 1.6Hz) 7.76 (1H, d, J= 7.6Hz), 7.18- 7.20 (2H, m), 7.78 (1H, s), and 7.93 (1H, s) example 936-chloro-[3-(3, 4-methylenedioxyphenyl) propyl] benzimidazole [0476]
[Formula 180]
[0477] - Molecular formula ; C17H15ClN2O2, yield (%);40 and melting point (degree-C);107 - 109, and Mass m/e ; 315 (MH+) and NMR delta (CDCl3); [2.13-2.21 (2H, m),] 2.54 (2H, t, J= 7.4Hz) 4.11 (2H, t, J= 7.2Hz), 5.94 (2H, s) 6.59 (1H, dd, J= 8.0Hz, 1.6Hz), 6.64 (1H, d, J= 1.6Hz) 6.75 (1H, d, J= 8.0Hz), 7.24 (1H, dd, J= 8.4Hz, 2.0Hz) 7.31 (1H, d, J= 2.0Hz), 7.71 (1H, d, J= 8.4Hz) 7.84 (1H, s) example 946-chloro-2-formyl-1-(3, 4-methylene dioxy benzyl) benzimidazole [0478]
[Formula 181]
[0479] - Molecular formula ; C16H11ClN2O3, yield (%);55 and melting point (degree-C);120 - 122, and Mass m/e ; 315 (MH+) and NMR delta (CDCl3); [5.71 (2H, s),] 5.93 (2H, s) 6.64 (1H, d, J= 1.6Hz), 6.70 (1H, dd, J= 7.6Hz, 1.6Hz) 6.75 (1H, d, J= 7.6Hz), 7.36 (1H, dd, J= 8.8Hz, 2.0Hz) 7.46 (1H, d, J= 2.0Hz), 7.86 (1H, d, J= 8.8Hz) 10.11 (1H, s) example 952-amino-6-chloro-1-(3, 4-methylene dioxy benzyl) benzimidazole [0480]
[Formula 182]
[0481] - Molecular formula ; C15H12ClN3O2, yield (%);10 and melting point (degree-C);223 - 224, and Mass m/e ; 302 (MH+) and NMR delta (DMSO-d6); [5.13 (2H, s),] 5.95 (2H, s), 6.68-6.71 (3H, m), 6.77 (1H, d, J= 1.6Hz), 6.84 (1H, d, J= 7.6Hz) 6.90 (1H, dd, J= 8.4Hz, 2.4Hz), 7.07 (1H, d, J= 8.4Hz), 7.18 (1H, d, J= 2.4Hz) and molecular formula ; C15H12ClN3O2, yield (%);10 and melting point (degree-C);223 - 224, and Mass m/e ; 302 (MH+) and NMR delta (DMSO-d6); [5.13 (2H, s),] 5.95 (2H, s), 6.68-6.71 (3H, m), 6.77 (1H, d, J= 1.6Hz), 6.84 (1H, d, J= 7.6Hz) 6.90 (1H, dd, J= 8.4Hz, 2.4Hz), 7.07 (1H, d, J= 8.4Hz) 7.18 (1H, d, J= 2.4Hz) example 966-chloro-2-(imidazole-1-

IRU)-1-(3, 4-methylene dioxy benzyl) benzimidazole [0482]
[Formula 183]
[0483] - Molecular formula ; C18H13ClN4O2, yield (%);41 and melting point (degree-C);127 - 129, and Mass m/e ; 353 (MH+) and NMR delta (CDCl3); [5.20 (2H, s),] 5.97 (2H, s), 6.48-6.50 (2H, m), 6.76 (1H, d, J= 7.2Hz), 7.23-7.35 (4H, m), 7.72 (1H, d, J= 8.4Hz), 7.89 (1H, s) example 972-(4-carboxy piperidino)-5-chloro-1-(3, 4-methylene dioxy benzyl) benzimidazole [0484]
[Formula 184]
[0485] - Molecular formula ; C21H20ClN3O4, yield (%);84 and melting point (degree-C);201 - 202, and Mass m/e ; 414 (MH+) and NMR delta (DMSO-d6); [1.64-1.77 (2H, m),] 1.84-1.90 (2H, m), 2.40-2.46 (1H, m), 2.92-3.00 (2H, m), 3.43-3.47 (2H, m), 5.15 (2H, s), 5.96 (2H, s), 6.60 (1H, dd, J= 8.0Hz, 1.6Hz), 6.72 (1H, d, J= 1.6Hz) 6.82 (1H, d, J= 8.0Hz), 7.03 (1H, dd, J= 8.4Hz, 2.0Hz) 7.18 (1H, d, J= 8.4Hz), 7.42 (1H, d, J= 2.0Hz) example 982-(4-carboxy piperidino)-6-chloro-1-(3, 4-methylene dioxy benzyl) benzimidazole [0486]
[Formula 185]
[0487] - Molecular formula ; C21H20ClN3O4 and the melting point (degree C); amorphous and Mass m/e ; 414 (MH+) and NMR delta (DMSO-d6); [1.70-1.79 (2H, m),] 1.80-1.89 (2H, m), 2.31-2.42 (1H, m), 2.90-2.97 (2H, m), 3.39-3.45 (2H, m), 5.15 (2H, s), 5.96 (2H, s), 6.61 (1H, d, J= 8.0Hz), 6.73 (1H, s) 6.83 (1H, d, J= 8.0Hz), The following compounds were obtained according to the approach of 7.06 (1H, dd, J= 8.4Hz, 2.0Hz), 7.30 (1H, d, J= 2.0Hz), and 99 to 7.38 (1H, d, J= 8.4Hz) example 108 examples 43-44.
[0488] Example 992-(4-carboxy piperidino)-4-(3, 5-dichloro-4-methoxybenzyl) amino-6-cyano quinazoline [0489]
[Formula 186]
[0490] - Molecular formula ; C23H21Cl2N5O3, yield (%);98, and melting point (degree-C);255 -256 (decomposition)
- Mass m/e ; 486(M+1)+ and NMR delta (DMSO-d6); [1.36 (2H, brm),] 1.80 (2H, brm), 2.52 (1H, m), 3.03 (2H, m), 3.78 (3H, s) 4.59 (2H, d, J= 6.0Hz), 4.59 (2H, brm) 7.29 (1H, d, J= 8.8Hz), 7.50 (2H, s) 7.75 (1H, dd, J= 8.8Hz, 1.6Hz), 8.53 (1H, d, J= 1.6Hz), 8.85 (1H, brt, J= 6.0Hz), 12.18 (1H, brs) examples 1002, 6-dichloro-4-(4-ethoxycarbonyl piperidino) quinazoline [0491]
[Formula 187]
[0492] - Molecular formula ; C16H17Cl2N3O2, yield (%);100 and melting point (degree-C);101 - 103, and Mass m/e ; 354 (M+1) and NMR delta (CDCl3); [1.30 (3H, t, J= 7.2Hz) 1.99 (2H, m),] 2.14 (2H, m), 2.69 (1H, m), 3.35 (2H, dt, J= 11.2Hz, 2.4Hz), 4.20 (2H, q, J= 7.2Hz) 4.31 (2H, dt, J= 13.6Hz, 3.6Hz), 7.67 (1H, dd, J= 8.8Hz, 2.2Hz) 7.76 (1H, d, J= 8.8Hz), 7.79 (1H, d, J= 2.2Hz) example 1012 - (4-(carboxy piperidino)-4-(3, 4-dihydroxy benzyl) amino-6-chloro quinazoline [0493])
[Formula 188]
[0494] - Molecular formula ; C21H21ClN4O4, yield (%);95, and melting point (degree-C);216 -218 (decomposition)
- Mass m/e ; 429 (MH+) and NMR delta (DMSO-d6); [1.38-1.47 (2H, m),] 1.80-1.84 (2H, m), 2.44-2.49 (1H, m), 2.93-3.00 (2H, m), 4.48 (2H, d, J= 5.6Hz), 4.57-4.61 (2H, m), 6.60-6.65 (2H, m), 6.74 (1H, d, J= 1.6Hz) 7.24 (1H, d, J= 8.8Hz), 7.46 (1H, dd, J= 8.8Hz, 2.0Hz) 8.15 (1H, d, J= 2.0Hz), 8.48 (1H, brs), 8.675 (1H, s), 8.75 (1H, s), 12.14 (1H, brs) examples 1022, 6-dichloro-4-(5-hydroxy pentyl) amino quinazoline [0495]
[Formula 189]
[0496] - Molecular formula ; C13H15Cl2N3O, yield (%);82 and melting point (degree-C);134 - 135, and Mass m/e ; 300(M+1)+ and NMR delta (CDCl3); [1.53 (2H, m),] 1.65 (2H, m), 1.76 (2H, m), 3.63 (2H, m), 3.66 (2H, m) 7.61 (1H, dd, J= 8.8Hz, 2.4Hz), 7.67 (1H, d, J= 8.8Hz), 7.85 (1H, brs), 8.20 (1H, d, J= 2.4Hz) example 1032-(4-carboxy piperidino)-4-(5-nit ROKISHI pentyl) amino-6-chloro quinazoline [0497]
[Formula 190]
[0498] - Molecular formula ; C19H24ClN5O5, yield (%);80, and melting point (degree-C);176 -179 (decomposition)
- Mass m/e ; 438 (MH+) and NMR delta (DMSO-d6); [1.34-2.00 (10H, m),] 2.57-2.64 (1H, m),

3.18-3.59 (4H, m), 4.44-4.58 (4H, m), 7.72-7.86 (2H, m), 8.39-8.41 (1H, m), 12.31 (2H, brs) example 1042-(carboxymethyl) methylamino-4-(3-pyridyl methyl) amino-6-chloro quinazoline
[0499]
[Formula 191]
[0500] - Molecular formula ; C17H16ClN5O2, yield (%);97 and melting point (degree-C);222 - 223, and Mass m/e ; 358 (M+1) and NMR delta (DMSO-d6); [3.10 (3H, s),] 4.22 (2H, brs), 4.63 (2H, brs), 7.31 (2H, m), 7.48 (1H, m), 7.72 (1H, m), 8.14 (1H, d, J= 2.4Hz), 8.43 (1H, d, J= 4.8Hz), 8.59 (1H, m), 8.66 (1H, brs) example 1052-[N-(3-carboxy propyl)-N-methylamino]-4-(3-pyridyl methyl) amino-6-chloro quinazoline [0501]
[Formula 192]
[0502] - Molecular formula ; C19H20ClN5O2, yield (%);41 and melting point (degree-C);110 - 112, and Mass m/e ; 386 (M+1) and NMR delta (DMSO-d6); [1.67 (2H, brs),] 2.09 (2H, m), 3.02 (3H, s), 3.53 (2H, t, J= 6.8Hz), 4.67 (2H, d, J= 5.6Hz) 7.24 (2H, d, J= 8.8Hz), 7.31 (1H, dd, J= 8.0Hz, 4.8Hz) 7.47 (1H, dd, J= 8.8Hz, 2.0Hz), 7.73 (1H, d, J= 8.0Hz) 8.13 (1H, d, J= 2.0Hz), 8.41 (1H, d, J= 4.8Hz), 8.58 (1H, s), 8.62 (1H, brs), 12.04 (1H, brs) example 1062-(4-carboxy piperidino)-4-(2-pyridyl methyl) amino-6-chloro quinazoline [0503]
[Formula 193]
[0504] - Molecular formula ; C20H20ClN5O2, yield (%);92 and melting point (degree-C);235 - 237, and Mass m/e ; 398 (M+1) and NMR delta (DMSO-d6); [1.25-1.45 (2H, m),] 1.71-1.83 (2H, m), 2.45-2.54 (1H, m), 2.93-3.10 (2H, m), 4.37-4.48 (2H, m), 4.77 (2H, d, J= 5.5Hz) 7.25 (1H, dd, J= 7.7Hz, 5.0Hz), 7.37 (1H, d, J= 7.7Hz) 7.48 (1H, brs), 7.63 (1H, brs) 7.73 (1H, td, J= 7.7Hz, 1.6Hz), 8.34 (1H, brs), 8.51 (1H, brd, J= 5.0Hz), 12.23 (1H, brs) example 1072-(4-carboxy piperidino)-4-(3-pyridyl methyl) amino-6-chloro quinazoline [0505]
[Formula 194]
[0506] - molecular formula ; C -- 20 -- H -- 20 -- ClN -- five -- O -- two - yield -- (-- % --) --; -- 93 - the melting point -- (-- degree C --) --; -- > -- 250 - Mass -- m/e ; 398 (M+1) and NMR delta (DMSO-d6);1.45-1.60 (2H, m) -- 1.84-1.97 (2H, m), 2.58-2.68 (1H, m), 3.25-3.45 (2H, m), 4.45-4.54 (2H, m), 4.80 (2H, d, J= 5.7Hz) 7.41 (1H, dd, J= 7.9Hz, 4.8Hz), 7.82 (1H, dd, J= 9.0Hz, 2.0Hz), 7.86-7.96 (2H, m), 8.50 (1H, d, J= 4.8Hz), 8.55 (1H, d, J= 1.6Hz), 8.69 (1H, s) example 1082-(4-carboxy piperidino)-4-(4-pyridyl methyl) amino-6-chloro quinazoline [0507]
[Formula 195]
[0508] - Molecular formula ; C20H20ClN5O2, yield (%);89 and melting point (degree-C);167 - 168, and Mass m/e ; 398 (M+1) and NMR delta (DMSO-d6); [1.24-1.36 (2H, m),] 1.68-1.77 (2H, m), 2.40-2.49 (1H, m), 2.86-2.96 (2H, m), 4.42-4.50 (2H, m), 4.66 (2H, d, J= 5.7Hz) 7.28 (1H, d, J= 9.0Hz), 7.34 (2H, d, J= 6.0Hz) 7.51 (1H, dd, J= 9.0Hz, 2.4Hz), The compound shown below was compounded by the approach of either 8.18 (1H, d, J= 2.4Hz), 8.47 (2H, d, J= 6.0Hz), 8.74 (1H, t, J= 5.7Hz) examples 109 - the 144 above.
[0509]
[Table 2]
[0510]
[Table 3]
[0511]
[Table 4]
[0512]
[Table 5]
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[Table 21]

[Translation done.]